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PRINCIPAL INVESTIGATOR: Dusten Macdonald, MD

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Dusten Macdonald, MD

E-Mail: hd7mac@gmail.com

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The Geneva Foundation
917 Pacific Ave, Suite 600
Tacoma, WA 98402

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14. ABSTRACT

This program established the infrastructure to provide state-of-the-art targeted radiation therapy to military personnel and veterans with cancer. The research aspect of this project demonstrated that 1) targeted radiation therapy with real-time localization and tracking allows use of a smaller planning treatment volume margin with a significant decrease in rectal and bladder volume treated and that the use of such targeted therapy can occur within standard treatment times and thus is feasible for routine clinical use, 2) Beacon® Transponder is of benefit in pelvic radiation therapy following prostatectomy by allowing reduction in bladder volume incorporated into treatment volume, 3) the precision and accuracy of radiation therapy using breath-hold technique for left-sided breast cancer patients treated with adjuvant radiation therapy, with the benefit of confirmatory tracking via the Calypso® 4D Localization System will help to spare toxicity to the heart, 4) a military medical center department, with essentially fixed costs, may feasibly apply advanced technologies and hypofractionation to palliative patients and 6) use of the Calypso system, and other advanced radiation therapy equipment, can improve treatment techniques and outcomes in malignancies arising in other parts of the body.

15. SUBJECT TERMS
Calypso, Prostate, Intensity Modulated Radiation Therapy (IMRT), Planning Target Volume (PTV), Beacon Transponders

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Targeted Radiation Therapy for Cancer Initiative Final Report

INTRODUCTION:
The full potential of radiation therapy has not been realized due to the inability to locate and track the tumor target continuously during the delivery of the radiation dose. Without the ability to accurately locate the tumor target at the time of dose delivery, more of the patient's healthy tissue is exposed to radiation, which may result in acute or chronic complications. The research studies and activities described in this report will improve the techniques of modern radiation therapy and directly benefit the Department of Defense by: providing improved, state-of-the-art prostate cancer treatments to active-duty military personnel and veterans; continuing to investigate reduction of the number of daily radiation treatments required for each patient, thereby reducing the cost of care and increasing treatment capacity within the military delivery system; enabling research to establish standards of care for targeted radiation therapy; establishing a DoD center of excellence in targeted radiation therapy; and accelerating the development of the targeted radiation therapy platform to treat additional cancers that significantly affect service personnel, their families, and veterans, such as breast cancer and metastatic cancer. The Calpyso® 4D Localization System is a FDA Class II device, utilized to track both inter-fraction and intra-fraction tumor movement in patients receiving radiation therapy for various malignancies.

BODY:

Task Completion

Task 1. *Establishment of centers for targeted radiation therapy at MAMC and VAPSHCS with installation of the Calypso® 4D Localization System.*

Installation of the Calypso® 4D Localization System occurred at MAMC in the fall of 2008. The radiation team at MAMC received training and technical support of the system as needed.

The installation and training of the Calypso System also occurred at VA Puget Sound Health Care System (VAPSHCS). However, no study patients were ever treated at the site secondary to site non-compliance with achieving the necessary technical capability to participate. The system was de-installed and moved to MAMC to be used in the newly renovated second vault with the new linear accelerator.

Task 2. *Treatment for prostate cancer with state-of-the-art technology to allow real-time localization and continuous tracking of the tumor target.*

A total of 42 non-study prostate cancer patients were treated with the Calypso system at MAMC. Non-protocol patients allowed providers to gain further proficiency with the Calypso unit. Seven of those patients were treated in the prone position. The experience and knowledge gained in this alternative positioning technique allowed for patients who

were not anatomically compatible with the Calypso system in the supine position to be able to receive treatment with this state-of-the-art localizing/tracking device. The Reduced Margins protocol was amended to allow for prone positioning and we treated three study patients in this position.

MAMC now routinely uses the approved FDA surface transponders off protocol to monitor breathing motion during our standard breath-hold technique for treating left-sided breast cancer, which allows sparing of the heart. We treated 100 off-protocol patients using these approved external beacons: 68 breast cancer patients, 28 Stereotactic Body Radiotherapy (SBRT) patients, and 4 non-SBRT lung cancer patients. The Calypso system provides a previously unavailable level of additional positional monitoring for these patients and we have gained considerable expertise with this technique.

Task 3. *Feasibility study with reduced planning treatment volume (PTV) margins and intensity modulated radiation therapy (IMRT) using targeted radiation therapy.*

A total of thirty-five participants consented and thirty-one enrolled in this study. Twenty-six of these subjects completed the trial including all follow-up visits through May 3, 2017. The final nine patients completed follow-up visits during the third quarter of project year 09. All subjects finished treatment; four were screen failures and never started treatment. Two patients died while in the follow-up phase: one from lung cancer, which was unrelated to the study, and the second from comorbidities which were also unrelated to the study. These two subjects completed study follow-up visits through Month 12 and Month 18 respectively. This study was closed to enrollment May 31, 2015 to allow for 12 months of follow-up to assess for toxicity prior to grant closure.

We gave five presentations at national conferences and two here at Madigan, supported by the data collected from this trial thus far (see Appendix for complete list of presentations and publications). We analyzed data endpoints as the final subjects complete the follow-up phase. Databases were created for the raw data gained from the Expanded Prostate Cancer Index Composite (EPIC) and International Prostate Symptom Score (IPSS) questionnaires as well as for Toxicity Sheet surveys, which were completed during specified pre-treatment, treatment, and follow-up visits through Month 24. A total of 1,224 IPSS, EPIC, and Toxicity surveys were completed and recorded. Additionally, the compiled 1,333 fraction logs contain almost 15,000 supplementary pieces of raw data.

Through analysis of part of this data, we found that reduced margins decreased the mean planning treatment volume by close to half (47.8%) which spared an average of 33.5Gy to the external and internal anal sphincter and rectum.

Reduced planning treatment volume margins resulted in minimized doses of radiation to healthy tissue which in turn lessens the chance of side effects and leads to better overall health outcomes. With our study, we have found that 83.9% of patients experienced physician-reported acute side effects and 51.6% experienced physician-reported late side effects. In general, side effects were mild. Only one patient (3.2%) experienced a grade 3 acute genitourinary side effect (urinary retention requiring TURP) and there were no

grade 3 or 4 gastrointestinal side effects. Likewise, only a small percentage of patients (9.68%) experienced late grade 2 GU and GI side effects.

The completed EPIC questionnaires have also shown that patients tolerated definitive radiation therapy with reduced PTV margins for prostate cancer very well. At the end of treatment, average EPIC scores reflected patients' recorded acute toxicity with bowel, urinary, and sexual function scores having dropped by 11%, 14%, and 7% respectively. By four months post treatment, EPIC scores showed average bowel and urinary functions had returned to within the range of baseline. EPIC sexual function scores showed the greatest lasting side effects 4 months post treatment as they remained 7% below baseline.

We analyzed the anorectal angle (ARA) of the 28 study patients who completed at least 12 months of follow-up. The ARA was measured on the mid-sagittal slice of each patient's treatment planning CT scan at the angle formed by the intersection of the central axes of the lower rectum and the anal canal. The mean angle measured was 104°. Having divided the sample cohort by the mean into two groups, "large ARA" and "small ARA", we found no statistically significant difference between small and large ARA in baseline EPIC bowel scores, nor in acute or chronic toxicity scores. Given this study data, there appears to be no association between larger ARA and increased bowel toxicity following radiation therapy for prostate cancer. This information adds depth to an earlier, exploratory study we performed to evaluate for an association between pre-treatment ARA and post-treatment bowel toxicity.

A manuscript titled "Evaluating the potential benefit of reduced PTV margins for low and intermediate risk prostate cancer patients using real-time electromagnetic tracking" is in the process of submission to the International Journal of Radiation Oncology Biology Physics. Contributors to this article are: Avinash R. Chaurasia, Kelly J. Sun, Christopher Premo, Timothy Brand, Brent Tinnel, Stacie Barczak, John Halligan, Joseph Brooks, Michael Brown, and Dusten Macdonald.

VAPSHC received full regulatory approval for this protocol, but never consented any subjects. This site is closed. In an effort to boost enrollment, we collaborated with Brooke Army Medical Center (BAMC) and added them as a site on this protocol. However, due to lack of enrollment BAMC was removed as a participating site effective April 9, 2015. The statistical significance of the data was not affected by this setback, as MAMC exceeded expected enrollment. This protocol was closed by the Pacific Regional Command IRB on July 14, 2017, and HRPO acknowledgment of the closure was received.

Task 4. *Become an RTOG member to better serve as a center of excellence.*

The Radiation Therapy Oncology Group (RTOG) is a recognized leader in working to increase survival and improve quality of life for cancer patients. We completed our task of becoming an RTOG member and were excited to open our first RTOG study as an affiliate member. Subsequently, we were informed that MAMC's parent site was acquired by a different group and felt they did not have the capability to maintain the

oversight needed to act as our parent as they are located in California. However, since Madigan falls under the cooperative group, Southwestern Oncology Group (SWOG), we were able to participate in certain RTOG studies encompassed within that group.

We opened RTOG 0924 (Androgen Deprivation Therapy and High Dose Radiotherapy With or Without Whole-Pelvic Radiotherapy in Unfavorable Intermediate or Favorable High Risk Prostate Cancer: A Phase III Randomized Trial) through SWOG. This is an important study for higher-risk prostate cancer patients which will help to answer important questions regarding necessary length of hormone therapy and the radiation target required for high-risk patients being treated with modern techniques. Participation in this study will help us to continue to establish MAMC as a "center of excellence" in targeted radiation therapy. Also, an added benefit with this trial is that it did not compete with our reduced PTV margins study. We did not have the opportunity to enroll any patients for this study.

Task 5. *A Randomized Study Comparing External Pelvic Immobilization to Limited Immobilization for the Treatment of Prostate Cancer with IMRT Using Real-Time, State-of-the-Art Motion Tracking with the Calypso® 4D Localization System.*

Sixteen subjects consented and thirteen of these were enrolled. All thirteen subjects completed the study from consent to one-year follow-up; three subjects were screen failures and never started treatment. Enrollment was closed June 30, 2015 to allow for the one-year follow-up period.

This study proved to be difficult to enroll since most patients who are intermediate to high-risk choose to have a prostatectomy. Our original goal of 20 subjects did not seem feasible based on our patient population. Our enrollment of 13 participants allowed us to gather enough data to support hypothesis-generating research.

VAPSHCS received partial regulatory approval. No subjects were ever consented. This site was closed.

We submitted one abstract for presentation based upon this protocol, but it was not accepted for presentation. This protocol was closed with the MAMC IRB on July 14, 2017 and closure documents were submitted to HRPO at that time.

Task 6. *Post-prostatectomy Daily Targeted Radiation Therapy Using Real-Time, State-of-the-Art Motion Tracking with the Calypso® 4D Localization System: A Feasibility Study.*

A total of twenty-five subjects were consented and twenty of these were enrolled; nineteen subjects completed the entire study, five were screen failures and one was withdrawn during treatment because of an inability to accurately localize him to Calypso due to an anatomical shift that was occurring when using his Calypso beacons.

The data gathered from this process enabled us to determine how much we can safely reduce the PTV margins for a follow-on reduced PTV margins study. The localization data captured from this protocol and from any future follow-on reduced PTV margins

protocols will eventually be analyzed in aggregate to provide the best possible data on localizing the prostatic fossa using Calypso beacons.

The database created for this study is in large part built around measurements and calculations which are based directly off daily subject cone beam computed tomography (CBCT) images. The location of the anterior rectal wall, the plane of symphysis pubis, and the posterior bladder wall on five equally spaced axial CBCT slices (interior, inferior-mid, middle, superior-mid, and superior) are recorded. In addition to this, the distances between each of these structures is calculated, the obturator internus muscles are measured on the middle slice, and the 3-dimentional location of the apex, Lbase, and Rbase beacons are recorded. All CBCT measurements are done before and after auto-fusing each CBCT scan with the treatment planning scan.

Daily changes in bowel and bladder position which are often affected by gas or feces in the rectum, the fullness of the bladder, etc., appears to be responsible for a large amount of the random motion tracked via beacon location. The average shifts from the beacon to CBCT-localized isocenter were 2.1mm, 2.0mm, 0.35mm, and 0.05° in the vertical, longitudinal, lateral, and rotational planes respectively.

A manuscript based on the data from this study was started by Madeera Kathpal, at the time an Army-funded Radiation Oncology resident at the Rutgers Robert Wood Johnson Medical School, and continued by Charlton Smith, a radiation oncology resident from the Uniformed Service University of the Health Sciences during his rotation at MAMC during March 2016. During this time and under the guidance of MAMC physicians, he focused on drafting the preliminary manuscript. Since that time, through the combined efforts of Dr. Dusten Macdonald and Charlton, the manuscript is now in the process of final editing prior to submission for publication. To date, we have presented a total of three poster presentations at national conferences as well as an oral presentation at Madigan's Research Day based on our work from this protocol.

This protocol was closed with the MAMC IRB on September 27, 2017, and submitted to HRPO for closure.

Task 6a. *Reduced PTV Margins Post-prostatectomy Daily Target Guided Radiotherapy Using Real-Time, State-of-the-Art Motion Tracking with the Calypso® 4D Localization System: A Feasibility Study*

The quantitative analysis of the cone-beam CT scan data collected from the original protocol outlined in Task 6 determined how much of the PTV margins can safely be reduced. We determined that using Calypso beacons for localization allowed us to safely spare approximately 1 cm of normal bladder, which is included in the clinical target volume (CTV) when treatments are localized with other techniques.

Our analysis of the CBCT data collected in Task 6 demonstrates that most patients would be appropriately treated with significantly decreased circumferential margins. However, a few patients are outliers who require more margin. It has been demonstrated by other

groups that these outliers can be identified by analysis of target volume coverage during the first five treatments, followed by margin adaptation based on this analysis. Therefore, our intention was to open a protocol which included an adaptive radiation therapy component, by which each patient's first five fractions of radiation therapy were analyzed for a pattern of excessive target volume motion, and margin adjustments were then made to the patient's radiation treatment plan if necessary. Unfortunately, secondary to expiration of funding, this protocol was never opened.

Task 7. *Central Dose Escalated Palliative Conformal Radiation Therapy*

The intention of this study was to include two phases with the potential to dramatically alter the efficiency and efficacy of palliative radiation therapy. The primary goal of this study was to develop and validate a set of dosing guidelines that would allow widespread use of advanced technology radiation therapy techniques, such as IMRT and Volumetric Modulated Arc Therapy (VMAT), in treating palliative patients. The main obstacle to overcome in reaching this goal was to establish practice patterns that allow simplified, though still safe, use of this technology in order to decrease the expense associated with these treatments. The first phase of this study involved a retrospective portion where we reviewed the patients treated palliatively here at MAMC, and the second phase was to prospectively evaluate the feasibility of this strategy with specific quality of life outcome measurements. We accomplished the first phase, but not the second.

We have evaluated all palliative patients treated between June 2006 and December 2007 and those treated from January 2013 to June 2014. A significant increase in average dose per fraction with a mean increase of 175cGy in the latter group was found. A 26% increase in the number of single fraction treatments and use of IMRT, VMAT, and Arc plans was also found. On the other hand, both the mean total dose per site and the mean number of fractions decreased; the mean total dose per site dropped by 676cGy. These changes represent the implementation of modern techniques when deemed necessary and beneficial to patients, in a setting less constrained by insurance billing practices. In addition, the increase in single fraction treatments represents a more cost-effective use of palliative radiation which follows consensus guidelines supported by randomized evidence.

Although new radiation therapy technologies are expensive, they open the door for increased use of multi-site palliation (MSP) in palliative patients. In modern practice, MSP provides cost benefits to patients when analyzed in terms of cost per treated site. In analyzing patients treated between January 2013 and June 2014, we found that the mean cost per site was significantly less in the MSP cohort compared to the cost of single site palliative (SSP) treatments. The mean cost per site for MSP and SSP was $2,220.09 and $4,552.68 respectively. We also found that when compared to SSP, MSP significantly decreased the daily treatment time per site by an average of three minutes and 40 seconds.

We compiled a database recording additional information for further work on this study which tracks any and all related side effects patients experienced and the volume of the primary lesion to better evaluate the lasting effects of radiation. Treatments were also broken down for billing purposes in order to analyze how the special financial circumstances surrounding a military facility may impact patient care.

Based on this research, we presented a poster based on our abstract, "Cost and Efficiency of Multi-Site Palliative Radiation Therapy" during the 2016 ASTRO Annual Meeting. We also presented "Change in Practice Patterns and Increasing Use of Modern Technology for Palliative treatments at a Military Hospital" at the 101st Scientific Assembly and Annual Meeting of the Radiological Society of North America (RSNA), as well as the 2016 Madigan Research Day. In addition, an abstract based on this data was presented at the 2016 Uniformed Services University of the Health Sciences Research Day.

This protocol was closed with the Pacific Regional Command IRB on September 22, 2017 and submitted for HRPO closure at that time.

Task 8. *A Retrospective Study of Breast and Chest Wall Positioning During Whole Breast Radiation Therapy for Left-Sided Breast Cancer Using Breath-Hold Technique Supplemented by Motion Tracking with the Calypso® 4D Localization System.*

This study examined the precision and accuracy of radiation therapy using breath-hold technique for left-sided breast cancer patients treated with adjuvant radiation therapy, with the benefit of confirmatory tracking via the Calypso® 4D Localization System.

We conclude that this technique demonstrates accuracy and precision that is well within the traditional 1 cm margin of error, allowing a potential decrease in planning margins.

As with all other projects, we created a digital database containing all raw data for this retrospective study. This database contains approximately 97,000 pieces of raw data representing numerous measurements taken from Calypso® reports and calculations based on these measurements. From this data we showed that using the deep inspiration breath hold technique in conjunction with external beacon tracking significantly reduced mean heart (MH) and left anterior descending coronary artery (LAD) dose compared to free breathing plans. This technique decreased MH dose by 55.7% and LAD dose dropped by 69.8% which equates to approximately 14.24±5.8 Gy spared in these areas.

The coaching from technicians based on real-time Calypso® tracings which helped patients to have reproducible breath holds allowed for the beam-on times of treatment to occur in a very precise window in comparison to the breath hold as a whole. As a result, in each dimension, chest wall (CW) excursion during the entire breath hold was significantly greater than CW excursion during beam-on time. Average CW excursion was decreased by 56% laterally, 66% longitudinally, and by 69% vertically. Treatment was paused in 23% of fractions to adjust for suboptimal breath hold or CW position. While this added a small amount to the treatment time, it was ideal for patients as it

ensured that treatment was limited to the most stable portion of the deep inspirational breath hold plateau, significantly reducing intra-fraction motion. Interestingly, only three patients, or 20% of the study cohort, accounted for more than 67% of all beam holds.

We found that electromagnetic confirmation of CW position allows for verification of breath hold reproducibility to within 3.1mm in 95% of fractions. We determined that the CW is not necessarily stable during deep inspiration breath hold, but that the use of electromagnetic confirmation of CW position is technically feasible and allows for potential improvement in accurate delivery of adjuvant radiation therapy for left breast cancer.

We included 15 patients on our retrospective protocol. Three poster presentations based on our work were presented at two different national conferences in September 2014. MAJ Madeera Kathpal's contributions during her residency rotations with us on this project were instrumental to its overall success. We also gave an oral presentation at Madigan Research Day on April 24, 2015. Our manuscript entitled, "Deep Inspiration Breath Hold with Electromagnetic Confirmation of Chest Wall Position for Adjuvant Therapy of Left-Sided Breast Cancer: Technique and Accuracy," which we submitted to the Journal of Practical Radiation Oncology (PRO) based on this research, was published in the September 2016 issue of PRO.

Following the acceptance of our manuscript for publication, which was based on the final analysis of data for this study, the Retrospective Study of Breast and Chest Wall Positioning During Whole Breast Radiation Therapy for Left-Sided Breast Cancer Using Breath-Hold Technique Supplemented by Motion Tracking with the Calypso® 4D Localization System was closed. Closure was approved though MAMC IRB August 10, 2016. This closure was reported to HRPO.

Task 9. *Establish a center of excellence for targeted radiation therapy. The intent of this task is to create a facility specialized in all modalities of targeted radiation therapy such as cone beam CT, on board kilovoltage orthogonal imaging, and the Calypso® 4D Localization System.*

The staff at MAMC have treated 213 patients with the Calypso® 4D Localization System and continue to develop expertise as a center of excellence in targeted radiation therapy. This grant facilitated continuing medical education for the staff at MAMC on image guided radiotherapy.

Active duty Army Radiation Oncologist resident Madeera Kathpal completed her fifth and final rotation at MAMC in September 2014. This resident learned advanced tumor targeting techniques with the Calypso system and assisted in evaluating data and writing scientific papers under the guidance of the MAMC physicians. MAJ Kathpal worked on many projects under the guidance of MAMC physicians, including analyzing data from the post-prostatectomy trial and then writing/presenting three abstracts based on the findings at two national conferences and at Madigan's Research Day. She also contributed in developing our retrospective breast protocol as well as writing/presenting three abstracts at two different national meetings based on our data analysis. In addition

to this, MAJ Kathpal was a key part in developing and writing our recently submitted manuscript. Dr. Kathpal is now an attending radiation oncologist at the Fort Belvoir military treatment facility in Virginia. We hope to collaborate with her in the future as she is very interested in initiating research in targeted radiation therapy at her new facility.

In addition to MAJ Kathpal, we had a MAMC Radiology resident, four medical students on research rotations, a pre-medical student, and two radiation oncology residents assist in evaluating, preparing and writing abstracts based on the data gathered in our Reduced PTV Margins, Post-Prostatectomy, Immobilization, and Palliative protocols.

We also had two undergraduate Geneva Foundation research interns contribute to our research efforts, as well as two third-year Uniformed Services University (USU) medical students. Additionally, we had the opportunity to collaborate with two medical oncology colleagues, Anthony Fadell, MD and Penelope Harris, MD. The combined effort of all involved made possible the numerous presentations and publications that have been a result of this grant-supported study.

On July 28, 2014, Dr. Bruce Montgomery, a professor of medicine and physician at the University of Washington and Seattle Cancer Care Alliance spoke at our annual symposium on 'Recent Innovations in the Treatment of Metastatic Castrate Resistant Prostate Cancer'. The targeted audiences for this symposium were urologists, urology residents, radiation oncologists, and medical oncologists, internal medicine residents as well as some scientists from the Madigan Department of Clinical Investigation.

We hosted eight educational conferences/visiting professorships in the area of urology and radiation oncology during the period of performance of this grant. We believe these annual educational events promoted our site as a "center of excellence in targeted radiation therapy" and encouraged physicians in the community to seek our expertise. On July 17, 2016 Dr. Ian Thompson, Director of the Cancer Therapy and Research Center of the University of Texas Health Science Center in San Antonio, discussed, 'Adaptive Trials and Other Modern Approaches to Cancer Therapeutic Trial Design'. The targeted audiences for this symposium were urologists, urology residents, radiation oncologists, and ancillary staff. Dr. Thompson's lecture was highly relatable to the work we were doing at MAMC and prompted much attendee participation and discussion.

Our eighth and final event was held on July 21, 2017. Dr. Martin Gleave presented a lecture titled "Telling Tales of Precision Oncology in mCRPC." Dr. Gleave is a Professor and Chairman of the Department of Urologic Sciences at the University of British Columbia, as well as Co-Founder and Director of the Vancouver Prostate Center. He has published over 450 papers which have been cited over 28,000 times, helping to attract more than $90M in research funding. Dr. Gleave's lecture was well received and prompted much discussion among attendees.

We collected information regarding problems/challenges encountered with Calypso as a "Lessons Learned Log" which identifies the problems encountered with possible causes

and the techniques used to solve the problem. The physicist at our site gave an oral presentation about the Calypso System at a professional physics conference in October 2013. She incorporated some of our "lessons learned" information in her speech.

We also used the Calypso System with surface transponders while treating lung cancer patients with stereotactic body radiation therapy (SBRT). SBRT is a type of radiation therapy in which a few very high doses of radiation are delivered to small, well-defined tumors. The goal is to deliver a radiation dose that is high enough to kill the cancer while minimizing exposure to surrounding healthy organs. We successfully treated 28 patients using the Calypso System to track breathing motion. We are very excited to be incorporating this technique with SBRT and believe it supports our overarching goal in establishing a center of excellence for targeted radiation therapy.

We are currently working to develop methods and procedures for stereotactic radiosurgery (SRS) to include use of the Calypso System as well. This will further advance MAMC as a center of excellence for targeted radiation therapy.

The final resident who completed a rotation in Radiation Oncology at Madigan was Dr. Avinash Chaurasia. Dr. Chaurasia contributed to our goal of establishing a center of excellence by contributing to data analysis and manuscript creation. These rotations, under the guidance of MAMC physicians, provided an opportunity for residents to gain research experience with nearly complete data sets provided. Dr. Chaurasia began his rotation in June of 2017 and completed it that July.

Task 10. *Present finding of feasibility studies at professional conference.*

We presented a poster presentation based on the initial findings of the Reduced PTV margins feasibility study at the ASCO/ASTRO/SUO Genitourinary Oncology Symposium in February 2012. Two of the authors attended the conference and presented the poster. We received positive remarks and feedback on this early study which demonstrated the potential impact of reducing PTV margins and also described a detailed method for tracking dose to the muscles of the pelvic floor.

We presented a total of nine poster presentations at two prominent medical symposiums based on the continued findings of our research. This marks a total of 9 presentations at professional conferences.

On a national level, abstracts were presented via poster at ACRO, RSNA, and ACRO annual meetings. Locally, abstracts were presented at both MAMC and USUHS research days. In addition, the Journal of *Practical Radiation Oncology* published our manuscript online in January 2016. When tallied with past presentations, we have presented a total of 13 poster presentations and one oral presentation, and had one abstract published at seven prominent medical symposiums based on the continued findings of our research. Also mentioned prior in this report, we have given three oral presentations and two poster presentations at Madigan Research Day events. One manuscript based on our findings

has also been published. We presented on our palliative research at the American Society for Radiation Oncology (ASTRO) 2016 annual conference.

Problem Areas

It was unanimously decided to discontinue efforts at VAPSHCS based on several factors, including: radiation therapy staffing issues at the VA; the slow pace of the VA IRB system; and, most fundamentally, the practice pattern of the Seattle VA, which focuses on brachytherapy as treatment for prostate cancer. It seemed unlikely patient accrual would substantially contribute to our research. The SOW was updated to remove the VA.

BAMC did not enroll any participants on The Reduced PTV Margins study. As stated previously, BAMC decided to close-out the study at their site due to lack of enrollment. Fortunately, we were able to come close to meeting our enrollment goals at MAMC and do not view the BAMC closure as a setback to the project.

Our RTOG affiliate membership was discontinued as stated in task 4. Since our parent site was acquired by a different group they felt they did not have the capability to maintain the oversight needed to act as our parent since they are located in CA. RTOG agreed and removed us as an affiliate. However, since Madigan falls under the cooperative group, SWOG (southwestern oncology group), we are able to participate in RTOG studies that are encompassed with SWOG.

KEY RESEARCH ACCOMPLISHMENTS:

- Enrolled 31 on the Reduced PTV Margins protocol
- Enrolled 13 subjects on the Immobilization protocol
- Enrolled 20 subjects on the Post-Prostatectomy protocol
- Treated 124 non-study patients with Calypso (including prostate, breast, SBRT and lung)
- Analyzed data on 15 patients enrolled in the retrospective breast cancer study
- Developed a database of volumetric and dosimetric anatomical data correlated with patient quality of life outcomes for patients treated on the reduced PTV margins study.
- Developed a database of anatomical data describing quantitatively the morphology of the prostatic fossa measured on over 500 treatment-matched CT scans in post-prostatectomy patients receiving radiation therapy
- Built a database categorizing the cost and treatment time for 2,959 palliative fractions delivered to 156 patients in addition to survivorship of all palliative patients treated between June 2006 and December 2007 and January 2013 to June 2014.
- Constructed a database to track patient excursion and treatment time for more than 550 fractions delivered under the Immobilization study.
- Created a database tracking precise breathing motion and breath hold stability in three axes in left-sided breast cancer patients.

- Continued development of Madigan as a center of excellence in Targeted Radiation therapy, including continued success of our annual multidisciplinary educational conference/visiting professorship.
- Developed technical expertise in using Calypso surface beacons to track breathing motion in left-sided breast cancer, allowing sparing of the heart.
- Developed procedures for using Calypso surface beacons to track breathing motion in stereotactic body radiation therapy lung cancer patients thus minimizing radiation to surrounding healthy organs.
- Presented our research findings orally and in poster form at national conferences and Madigan Research Day.

REPORTABLE OUTCOMES:

- Our site was acknowledged in two print articles which ran in the Ranger (a local newspaper that targets military retirees) and the Mountaineer (a paper distributed within MAMC and to retirees and active duty). The articles included our growth and efficiency of the multidisciplinary prostate cancer clinic as well as our affiliation with research and the Calypso System.
- Abstract title: "Dose to the Muscles of Fecal Continence During Radiation Therapy for Prostate Cancer Using Calypso Localization." Poster was presented at the ASCO/ASTRO/SUO Genitourinary Oncology Symposium in February 2012.
- Abstract title: "Dose to the Muscles of Fecal Continence During Radiation Therapy for Prostate Cancer Using Calypso Localization." Poster was presented at the ASCO/ASTRO/SUO Genitourinary Oncology Symposium in February 2012.
- Abstract title: "Anorectal Angle is Associated With Bowel Toxicity One Month Following Radiation Therapy for Prostate Cancer." Poster was presented at the ASTRO/RSNA 2013 Cancer Imaging and Radiation Therapy Symposium.
- Abstract title: "The use of electromagnetic transponder beacons to reduce planning target volume (PTV) margins in post-prostatectomy patients undergoing adjuvant or salvage radiation therapy." Poster was presented at the ASCO/ASTRO 2013 Genitourinary Cancers Symposium.
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- Kathpal M, Tinnel B, Sun K, Ninneman S, Malmer C, Wendt S, Buff S, Valentich D, Gossweiler M, Macdonald D. *Deep Inspiration Breath Hold With Electromagnetic Confirmation of Chest Wall Position for Adjuvant Therapy of Left-Sided Breast Cancer: Technique and Accuracy.* Pract Radiat Oncol. 2016 Sep-Oct;6(5):e195-202.

- Mitchell D, Tinnel B, Brand T, Huang R, Gossweiler M, Ninneman S, Wendt S, Macdonald D. Anorectal Angle and Bowel Toxicity Following Radiation Therapy for Prostate Cancer. American College of Radiation Oncology Annual Meeting, Mar 2016, Orlando, FL.
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- Sun K, Kathpal M, Tinnel B, Brand T, Ninneman S, Hughs G, Halligan J, Brown M, Brooks J, Macdonald D. Prostate cancer radiation therapy with reduced planning target volume (PTV) margins. 2015 ASCO/ASTRO/SUO Genitourinary Cancers Symposium, Orlando, FL.
- Sun K, Brand T, Hughs G, Halligan J, Tinnel B, Macdonald D. Reduced Planning Target Volume (PTV) Margins with Real-Time Electromagnetic Tracking During Definitive Radiation Therapy for Prostate Cancer. 2014 Western Section American Urological Society meeting, Maui, HI.
- Kathpal M, Sun K, Malmer C, Ninneman S, Wendt S, Hughs G, Macdonald D, Tinnel B. Deep Inspiration Breath Hold (DIBH) With Electromagnetic Surface Transponder Confirmation of Chest Wall (CW) Position During Radiation for Left Breast Cancer. 2014 ASCO Breast Symposium San Francisco, CA.
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- Kathpal M, Ninneman S, Huang R, Wendt S, Malmer C, Brand T, Halligan J, Brooks J, Brown M, Tinnel B, Macdonald D. The use of electromagnetic transponder beacons to reduce planning target volume (PTV) margins in post-prostatectomy patients undergoing adjuvant or salvage radiation therapy. 2013 ASCO/ASTRO/SUO Genitourinary Cancers Symposium, Orlando, FL.
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  See appendices for all abstracts presented to date as well as a complete listing of all presentations to date for ease of reference.

  Individuals Supported by this Grant
  Stephanie Ninneman, Research Program Manager
  Adam Waggoner, Research Assistant
  Stacie Barczak, Clinical Research Coordinator
  Geromy Morgan, Research Assistant
  Kenna Valentich, Research Intern
  Emily Clark, Clinical Research Coordinator

CONCLUSION:

The "Targeted Radiation Therapy for Cancer Initiative" has provided a framework for developing Madigan Radiation Oncology into a center of excellence for targeted radiation therapy.

Analysis of our database of post-prostatectomy anatomical information in over 500 treatment fractions allowed an unprecedented look at the inter- and intra- fraction changes in morphology of the prostatic fossa. Our planned participation in SWOG-encompassed protocols will allow us to contribute our expertise with Calypso localization to national research. Final cumulative analysis is leading to important quality of life outcomes publications in prostate cancer.

The research and education opportunities afforded by this progress have not gone unnoticed. On one of our abstract submissions, we had the opportunity to collaborate with the MAMC Radiology Department, a collaboration which we hope will expand. We also included members of the Pathology Department in our visiting professorships, including a substantial number of primary care providers in our visiting professorships over the years as well as medical

oncologists, and we hope to continue to foster future research collaboration with these groups. We worked closely with MAMC urologists to refine techniques and management strategies for our entire cohort of prostate cancer patients.

As discussed in this report, we are moving toward exciting new areas of research, including use of Calypso beacons to track breathing motion in breast cancer and lung cancer patients and using targeted radiation therapy modalities to improve our decades-old methods for treating metastatic lesions in the palliative setting. In addition to these areas of investigation, we also envision in the distant future developing expertise with Calypso beacons implanted in the lung and other sites.

This is an exciting era for targeted radiation therapy. With the help of the Congressionally Directed Medical Research Program we plan to treat our patients – military servicemen and women and their families – with lifesaving technology at the forefront of our field for years to come.

REFERENCES: N/A

APPENDICES:

Papers published or in the process of publication:

1. Chaurasia A, Sun K, Premo C, Brand T, Tinnel B, Barczak S, Halligan J, Brooks J, Brown M, Macdonald D. *Evaluating the potential benefit of reduced PTV margins for low and intermediate risk prostate cancer patients using real-time electromagnetic tracking.* In process of submission to International Journal of Radiation Oncology Biology Physics.

2. Kathpal M, Tinnel B, Sun K, Ninneman S, Malmer C, Wendt S, Buff S, Valentich D, Gossweiler M, Macdonald D. *Deep Inspiration Breath Hold With Electromagnetic Confirmation of Chest Wall Position for Adjuvant Therapy of Left-Sided Breast Cancer: Technique and Accuracy.* Pract Radiat Oncol. 2016 Sep-Oct;6(5):e195-202.

Abstracts and Presentations:

3. Mitchell D, Tinnel B, Brand T, Huang R, Gossweiler M, Ninneman S, Wendt S, Macdonald D. Anorectal Angle and Bowel Toxicity Following Radiation Therapy for Prostate Cancer. American College of Radiation Oncology Annual Meeting, Mar 2016, Orlando, FL.

4. Premo C, Tinnel B, Collins M, Ninneman S, Kathpal M, Buff S, Ahrmendi J, Stanke A, Valentich D, Macdonald D. Change in Practice Patterns and Increasing Use of Modern

Technology for Palliative Treatments at a Military Hospital. 101st Radiological Society of North American Annual Meeting, Dec 2015, Chicago, IL.

5. Macdonald D, Ninneman S, Tinnel B. Disruptive Innovation in Proton Therapy. Annual Conference of the Particle Therapy Co-Operative Group, May 2015, San Diego, CA.

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13. Kathpal M, Ninneman S, Huang R, Wendt S, Malmer C, Brand T, Halligan J, Brooks J, Brown M, Tinnel B, Macdonald D. The use of electromagnetic transponder beacons to

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14. Gossweiler M, Waggoner A, Huang R, Ninneman S, Hughs G, Wendt S, Brown M, Tinnel B, Macdonald D. Anorectal Angle is Associated With Bowel Toxicity One Month Following Radiation Therapy for Prostate Cancer. 2013 ASTRO/RSNA Cancer Imaging and Radiation Therapy Symposium, Orlando, FL. Pract Radiat Oncol. 2013 Apr-Jun;3(2 Suppl 1):S9.

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Appendix 1

Evaluating the potential benefit of reduced PTV margins for low and intermediate risk prostate cancer patients using real-time electromagnetic tracking

Avinash R. Chaurasia, Kelly J. Sun, Christopher Premo, Timothy Brand, Brent Tinnel, Stacie Barczak, John Halligan, Joseph Brooks, Michael Brown, Dusten Macdonald

Abstract (300 words):

Purpose

To quantify and describe feasibility, clinical outcomes, and patient reported outcomes of reduced planning target volume (PTV) margins for prostate cancer treatment using real-time continuous intrafraction monitoring with implanted radiofrequency transponder beacons.

Methods and Materials

On this prospective, IRB-approved study the Calypso™ localization system was used for intrafraction target localization in 31 patients with PTV margin reduced to 3 mm in all directions. A total of 1,333 fractions were analyzed with respect to movement of the prostate, pauses and interruptions, and dosimetric data. Pre- and post- treatment quality of life scores were tracked at baseline, during treatment, and up to 24 months after treatment.

Results

The mean time of daily treatment was 10.0 minutes, with 96.1% of all treatments falling within a 20-minute treatment window standard. On average, beacon motion exceeded 3mm during active treatment only 1.76% of the time. The average length of treatment interruption was 34.2 seconds, with an average of 1 interruption every 3.39 fractions. Displacement or excursion of tthe prostate was greatest in the superior/inferior dimension (0.11 mm/0.09 mm) and anterior/posterior dimension (0.07 mm/0.13 mm), followed by the left/right dimension (0.05 mm/0.06 mm). At 6 months, patients demonstrated a smaller change in Expanded Prostate Cancer Index Composite (EPIC) scores than the ProtecT comparator group (decreased short-term morbidity). However, in the Bowel and Urinary domains at 12 and 24 months, there was no significant difference.

Conclusion

Our data confirms and supports that using Calypso™ tracking with intensity modulated radiation therapy (IMRT) reliably provides minimal disruption to daily treatments and overall time of treatment, with the PTV only moving outside of a 3 mm margin < 2% of the time. Use of a 3 mm PTV margin provides adequate dosimetric coverage while minimizing genitourinary (GU) and gastrointestinal (GI) toxicity.

Introduction

Radiation therapy is an effective treatment option for many men with localized prostate cancer. The use of advanced radiation techniques including intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) have been shown to reduce gastrointestinal (GI) and genitourinary (GU) toxicities, even in the setting of dose escalation [1-3]. The addition of daily image guided radiotherapy (IGRT) has led to a further reduction in the dose to adjacent organs at risk (OAR) and improved toxicity rates by reducing planning target volume (PTV) margins [4]. Several systems have been devised to more precisely localize the target compared with skin markings, including daily ultrasound localization, cone beam computed tomography (CBCT) and implanted fiducial markers/gold seeds with daily orthogonal pretreatment portal imaging. Implementation of these methods have allowed reduction in PTV expansion to 5-7 mm [5-7].

In the past decade, there has been increasing research into intrafraction motion of the prostate as it relates to changes in treatment planning, dosimetry, and radiation-associated toxicities [8-20]. However, PTV margins still vary widely depending on immobilization and IGRT technique. Recent protocols have mandated PTV margins of 5-10mm, and only in the setting of extremely hypofractionated radiation therapy (SBRT) have margins of less than 5mm been considered acceptable in most practices [21]. Many institutions are now using a 5 mm posterior expansion in the setting of IGRT with conventional fractionation. Real-time electromagnetic tracking of the prostate allows real-time tracking of internal organ and patient movement, which can allow a further decrease in PTV margin. In theory, this would lead to a reduction in doses to adjacent organs at risk and reduction in late toxicities.

The current study is a prospective trial using the Calypso® 4D Localization System to treat prostate cancer patient volunteers with a CTV to PTV margin of only 3mm. We evaluated the feasibility, clinical outcomes, and patient reported quality of life outcomes of reduced PTV margins for prostate cancer treatments using real-time continuous intrafraction monitoring with implanted radiofrequency transponder beacons.

Methods and Materials

Patient Population: Men with low or intermediate risk prostate cancer per National Comprehensive Cancer Network (NCCN) risk groups were treated with definitive IMRT using reduced PTV margins on a prospective single-institution study. Eligibility criteria included: age > 40, histologically confirmed prostate adenocarcinoma, cT1a-cT2c, GS $\leq$ 7, PSA $\leq$ 15, and Zubrod performance score of 0 or 1. Those with high risk (per NCCN), node positive, or metastatic disease were excluded, as were patients with history of abdominoperineal resection, connective tissue disease or inflammatory bowel disease, HIV infection, chronic prostatitis or cystitis, history of bleeding disorder, active implanted devices such as pacemakers, prosthetic implants in the pelvic region which contained metal, or prior prostate cancer treatments other than androgen deprivation therapy. Patients with maximum anterior-posterior separation through

the torso minus the height of the center of the prostate greater than 17cm were excluded as well for technical reasons.

We obtained approval from our Institutional Review Board (IRB) as well as our Ethics Committee. Patients were consented prior to enrollment in this trial.

Treatment Planning and Margins: Three Calypso Beacon Transponders were implanted in the prostate via rectal ultrasound (US) guidance as per the manufacturer's instructions 4-7 days prior to CT simulation. CT simulation was performed with a full bladder and empty rectum. Lower extremity Vac-Lok bags were used for immobilization. The normal tissues were contoured as per RTOG guidelines. The gross tumor volume (GTV) was defined as the entire prostate. The apex was defined by either prostate MRI or urethrogram. For men with low risk prostate cancer, the clinical target volume (CTV) = GTV with no expansion. For men with intermediate risk prostate cancer, the CTV = the prostate, proximal 1cm of the seminal vesicles, plus a 3 mm expansion of the prostate (minus rectum and bladder) to account for possible extraprostatic extension. PTV for all patients was a 3 mm uniform expansion from the CTV. The prescription dose was 77.4 Gy in 1.8 Gy fractions. The coverage goals included $V_{77.4\ Gy} \geq 100\%$ of the CTV and $V_{77.4\ Gy} \geq 98\%$ of the PTV. The max dose allowed to the bladder and rectum was 105% (81Gy). Other constraints for the rectum included: $V_{78\ Gy} \leq 5\%$ (and $V_{78\ Gy} < 10cc$), $V_{75\ Gy} \leq 15\%$, $V_{70\ Gy} \leq 25\%$, $V_{65\ Gy} \leq 35\%$, and $V_{50\ Gy} \leq 60\%$. Other constraints for the bladder included $V_{80\ Gy} \leq 15\%$, $V_{75\ Gy} \leq 25\%$, $V_{70\ Gy} \leq 35\%$, $V_{65\ Gy} \leq 50\%$. All patients received static field IMRT. VMAT was not used, as it was not fully implemented in the clinic at the time of the beginning of the trial.

Target Localization and Tracking: Treatments were delivered using the Calypso™ Beacons for localization and continuous real time tracking with the Calypso™ system. A 2 mm tracking threshold was utilized such that, if the beacons moved more than 2 mm from their planned position, the therapists intervened to pause the beam until either the beacons returned to an acceptable range on their own or the patient was realigned.

Patient Reported Outcomes: Patients completed the full Expanded Prostate Cancer Index Composite (EPIC) questionnaire [25] prior to radiation therapy, at week 5 of radiation therapy, at the last fraction of radiation therapy, as well as at months 3, 6, 12, 18, and 24 following the start of radiation therapy. Three key domains were assessed: bowel, urinary, and sexual function. We compared morbidity to ProtecT, a contemporary, well-studied cohort of patients who underwent prostate external beam radiation therapy [EBRT, three-dimensional conformal radiotherapy (3DCRT)] using conventional PTV margins [22]. Differences between baseline scores and follow-up EPIC scores were compared between our Calypso patients and ProtecT patients. Per previous analyses of EPIC scores in prostate cancer radiation therapy, a clinically relevant change in quality of life was defined as difference from baseline to follow-up that was greater than half a standard deviation of the baseline value [26].

Results

A total of 31 patients were enrolled in our single institution study between May 2009 and June 2015. Patient characteristics can be found in Table 1. A total of 1,333 fractions (or treatments)

were recorded during this time. Follow-up of patients ranged between 12-60 months with formal follow-up as part of the study of 15 months, with a mean follow-up time of 22.45 months.

The mean time of daily treatment was 10.0 minutes with a standard deviation of 4.80 minutes (minimum = 4 minutes, maximum =71 minutes). 96.1% of all treatments fell within the standard of a 20-minute treatment window. On average, the PTV only spent 1.76% ± 1.69% of beam-on time outside of the 2 mm treatment window.

The average length of a treatment interruption was 34.2 seconds, with an average number of interruptions of 0.30 interruptions per fraction, equivalent to an interruption every 3.39 fractions. Each interruption was either a pause, during which the prostate returned to within 2mm of its planned position on its own, or a reposition, which required a couch position intervention by the radiation therapist. The average length of a pause was 17.6 seconds, the median length was 6 seconds. The average reposition time was 40.5 seconds, with a median of 28.5 seconds. Given the disparity between the mean and median for both pauses and repositions, the data is likely skewed by outlier(s) and the median values are more indicative of common pause and reposition times. These data can be found summarized in Table 2.

The greatest variation in displacement or excursion of the prostate in three dimensions was in the superior/inferior dimension (maximum excursion of the prostate during beam-on 1.1 mm ± 0.9 mm/0.9 mm ± 0.9 mm) and anterior/posterior dimension (0.7 mm ± 1.1 mm/1.3 mm ± 0.7 mm). Left/right movement was found to a lesser degree (0.5 mm ± 0.6 mm/0.6 mm ± 0.6 mm). These data can be found summarized in Table 3 as well as compiled graphically in Figure 1.

All of the 31 patients were able to achieve a standard of 98% PTV coverage at 77.4 Gy, with a mean of 98.4% ± 0.5%. The mean rectal volumes at $V_{78\ Gy}$, $V_{75\ Gy,}$ and $V_{70\ Gy}$ were 2.7% ± 1.6%, 8.2% ± 3.2 %, and 14.2% ± 5.3% respectively. The mean bladder volumes at $V_{80\ Gy}$, $V_{75\ Gy,}$ and $V_{70\ Gy}$ were 1.0% ± 1.7%, 7.5% ± 4.2 %, and 10.8% ± 6.2% respectively. These data can be found summarized in Table 4.

EPIC questionnaire response rate during follow-up was 95%. Three volunteers stopped completing questionnaires after 6-18 months of follow-up and others did not fully complete every questionnaire. For each domain at baseline, our cohort had similar or slightly lower scores than the comparator group, indicating a higher prevalence of baseline symptoms impairing quality of life. At 6 months, our patients demonstrated smaller change in scores (indicating better health-related quality of life) than the comparator group in the bowel, urinary, and sexual domains, although this change was only statistically significant in the urinary and sexual domains (P=0.14, 0.03, <0.01, respectively). However, in the bowel and urinary domains at 12 and 24 months, the EPIC scores of the patients on the ProtecT trial returned closer to baseline levels, while our patient's scores continued to decrease or remained stable, such that there was no significant difference in the EPIC scores of the two groups in these domains. Additionally, in the sexual domain, our patients showed significantly smaller follow-up change in scores at all points of follow-up, although this comparison is confounded by the use of six months androgen deprivation therapy on the ProtecT trial.

In ProtecT cohort, at six months clinically meaningful decline is demonstrated in all 3 domains compared to clinically meaningful decline only in the bowel scores in our patient group at that time point. At subsequent time points patients in the ProtecT trial did not demonstrate clinically meaningful decline in urinary symptoms. Table 5 and Figure 2 summarize patient reported EPIC scores and changes from baseline for our patients and the radiotherapy arm of the ProtecT trial.

Discussion

In the recent ProtecT trial, it was found that, when compared to prostatectomy, EBRT had little effect on urinary continence, a stable long-term effect on sexual function, and a worsening effect on bowel function (with recovery except for increasing frequency of bloody stools) [22]. Of note, all men on the radiation arm of this trial also received ADT. Additionally, the radiation technique was 3DCRT. To improve EBRT's toxicity profile, many efforts have been made to improve techniques of radiation delivery including inter- and intrafraction monitoring to decrease dose delivery to organs at risk (OAR).

A common concern about smaller PTV margins is intrafraction motion. There is significant time between obtaining on board kV imaging (OBI) and the completion of the daily radiation fraction with multiple field IMRT plans, leaving more time for intrafraction motion. Using the same technology, Shelton et al. in their study of 37 patients demonstrated that treatment time was the strongest predictor of observed displacements and that VMAT was associated with reduced motion [23]. Langen et al. reported similar findings that the likelihood of prostate gland movement increased with time and emphasized the importance of initiating treatment quickly after initially imaging the patient as well as minimizing overall time of treatment to decrease the likelihood of prostate drift [13]. In a comparison of VMAT with electromagnetic tracking to IMRT with and without electromagnetic tracking, Hall et al. found that VMAT was associated with a decreased time of delivery per treatment. Additionally, they found that using VMAT with electromagnetic tracking did not cause a significantly different treatment time compared to previous methods overall (IMRT without electromagnetic tracking) [24]. Hall et al. had an average treatment time of 13.81 minutes with VMAT with Calypso™ tracking [24]. Our data shows a lesser mean treatment time of 10.0 minutes ± 4.80 minutes using the same technologies with IMRT. We suspect that by using VMAT, treatment times would be even shorter. Additionally, our data showed encouraging reproducibility, with 96.1% of all treatments falling within a standard treatment time of 20 minutes. Our data confirms and supports that using Calypso™ tracking is time-efficient and reproducible.

Our study is one of the first to demonstrate minimal disruption to daily treatments using this new technology. Langen et al. had only 17/550 fractions (3.1%) with interventions, however Langen's protocol did not dictate any interventions based on observed prostate displacement [13]. In a similar study for patients undergoing prostate SBRT with Calypso™ tracking, Lovelock et al. demonstrated an average of 1.74 interventions/fraction required, with an increase in time of dose delivery of approximately 65 seconds [12]. Even with strict margins of less than 2 mm to require an intervention, we only required one intervention every 3.39 fractions, with a mean added time of 34.2 seconds per intervention. Each pause (self-return of the prostate to within 2mm) was a median of 6 seconds long and each reposition was a median of 28.5 seconds in duration. It then appears that pauses do not contribute significantly to treatment time, while

repositions tend to be slightly longer. Additionally, we noted that in a few, rare instances, repositions required anywhere up to 5-8 minutes. However, given the relatively low rate of interventions (1 intervention every 3.39 fractions), and the relatively small amount of time added on average by either an intervention or pause, our data shows that Calypso™ tracking reliably provides minimal disruption to daily treatments and overall time of treatment.

Many previous studies have tracked prostate intrafraction motion and its displacement/excursion has been well described in the literature [8, 13-17, 20, 23]. Mayyas et al. used Calypso™ tracking and found standard deviations for intrafraction prostate motion of 1.3, 1.5, and 0.6 mm (2 standard deviation values would be 2.6, 3.0, and 1.2 mm) in the AP, SI, and LR directions respectively in a study of 27 patients [15]. Shelton et al. also found that shifts were greater in the AP and SI dimensions and were likely related to organ motion, and LR motion was less and was likely related to patient motion [23]. Langen et al. described that the prostate's displacement in all directions was > 3 mm 13.6% of the time and > 5 mm 3.3% of the time on average [13]. Lin et al. looked at respiratory-induced prostate motion and found an oscillatory pattern of the prostate in the AP and SI directions, with 99% of patients showing average respiratory-induced motion between 0.2-2.0 mm [19]. In our study, we found prostate motion similar to slightly lower than what has generally been described previously in the literature. This is in line with findings of Bell et al. in a smaller study with only 3 patients, with findings of mean intrafraction motion ≤ 0.2 cm in all directions [8]. Additionally, the prostate spent only 1.76% of the time outside of our planned tracking constraint of 2 mm. These are strong indicators that 3 mm margins are feasible and safe.

We would expect that a decrease in PTV margin would lead to a decrease in normal tissue toxicity. Michalski et al. showed that IMRT was associated with a reduction in acute gastrointestinal (GI) and genitourinary (GU) toxicity, and that keeping $V_{70\,Gy}$ and $V_{75\,Gy}$ less than 15% and 10% respectively was associated with lower rates of GI toxicity [2]. Our V_{70Gy} of 14.2% and $V_{75\,Gy}$ of 8.2% fell within these margins and would thus also be associated with a reduction in toxicities as described by Michalski et al.. Zelefsky et al. found that with interfraction monitoring using fiducial markers versus a similar non-IGRT cohort there was a significant reduction in late urinary toxicity [9]. While previous studies have focused on rectal toxicity, our bladder dosimetry data at $V_{80\,Gy}$, $V_{75\,Gy}$, $V_{70\,Gy}$ show values that are in line with modern dosimetry standards to decrease GU toxicity [21].

Patient reported health related outcomes measured by EPIC questionnaire were generally improved or similar when compared to the ProtecT radiotherapy arm. Most notably at 6 months follow-up the urinary domain was significant improved in our study and the changes in sexual function scores remained significantly better compared to ProtecT. While initial decrements were smaller in our study, the ProtecT radiotherapy cohort showed a trend to return closer to baseline while our study showed stability/small decrements in bowel and urinary scores throughout 24 months of follow-up. Modeling studies have previously estimated that 3mm PTV margins in prostate cancer can decrease rectal toxicities by reducing volume of acute normal tissue damage which can predict late tissue damage [27-28]. This may suggest that the decreased short-term morbidity observed in our study may translate to long-term improvements in morbidity that we were unable to observe in our smaller patient set.

Some of the observed differences in EPIC scores between our patients and those on the ProtecT trial may be related to the differences in technique, lower dose used in ProtecT trial (74 Gy in 37 fractions), and to the fact that all men on the radiation arm of the ProtecT trial were treated with short term androgen-deprivation therapy. ADT-related reduction in prostate size could lead to improved EPIC scores.

Our analysis of patient reported health related outcomes compared to the ProtecT Radiotherapy arm is consistent with previous analyses of our cohort to the AIM and Prost-QA studies [26, 32] where pre-treatment and post-treatment EPIC-26 survey scores for bowel, urinary irritation/incontinence, and sexual function were compared [33]. Clinically meaningful decline was demonstrated in 2, 1, and 3 domains in our study, AIM, and Prost-QA cohorts, respectively, as shown in Figure 6. Furthermore, mean decrements between pre- and post-treatment scores were significantly lower in the AIM study compared to our cohort in the urinary irritation domain ($p=0.0009$). Our cohort's results were most similar to the Prost-QA patients, but worse than the AIM non-NHT study cohort in the urinary irritation domain.

Upcoming areas of interest include hypofractionation of localized prostate cancer treatment, as prospective trials, such as the Conventional versus Hypofractionated High-Dose Intensity Modulated Radiotherapy for Prostate Cancer trial (CHHiP) have shown non-inferiority of hypofractionated treatment and the possibility to decrease toxicities [30-31]. Further areas of study include the study of intrafraction monitoring in the setting of hypofractionated treatments, and prostate SBRT. As concern remains about late toxicities in these treatment regimens, one way to help reduce this may be with smaller PTV margins and tighter rectal/bladder constraints.

Limitations of our study include the relative small size of the patient population and the study being performed at a single institution. Future studies looking at incorporating larger patient populations and more treatment centers may point towards more generalizable ways of incorporating Calypso™ tracking into routine dosimetric planning and daily treatments.

Conclusion

Our data confirms and supports using Calypso™ tracking to reliably provide minimal disruption to daily treatments and overall time of treatment, with the PTV only moving outside of a 3 mm margin < 2% of the time. IMRT with Calypso™ tracking presents an effective way track the prostate in real-time. Using 3 mm PTV margins provides adequate dosimetric coverage while also minimizing GU and GI toxicity. Our decreased observed short-term morbidity may translate to long-term improvements in morbidity that we were unable to observe in our smaller patient set. Hypofractionation and prostate SBRT are ongoing areas of research to which Calypso™ tracking with reduced PTV margins may serve as an important tool to improve accuracy and minimize toxicity.

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Table 1. Patient Characteristics

Study	*******	**ProtecT**	**AIM**	**PROST-QA**
Number Enrolled	31	545	64	153
Age				
Median (y)	69		69	69
Range (y)	50-82		55-86	47-83
Age Group	no. (%)			
<60	3 (10)		3 (5)	22 (14)
60-69	14 (45)		35 (55)	66 (43)
≥70	14 (45)		26 (41)	65 (42)
PSA	(ng/mL)			
Mean	5.8 (± 2.6)		8.3 (± 6.2)	6.8 (±4.3)
Median	5.79	4.8	6.7	5.8
Range	1.5-11.3		0.6-36.8	0.5-25.8
Group	no. (%)			
<4 ng/mL	7 (23)		9 (14)	31 (20)
4-10 ng/mL	22 (71)		41 (64)	96 (63)
>10 ng/mL	2 (6)		14 (22)	26 (17)
Androgen Deprivation Therapy				
Yes	0		21	0
No	31		43	153
Gleason Score on biopsy	no. (%)			
<7	12 (39)	423 (78)	32 (5)	97 (63)
7	19 (61)	108 (20)	26 (41)	56 (37)
>7	0 (0)	14 (3)	6 (9)	0 (0)
Clinical stage	no. (%)			
T1	20 (65)	429 (79)	32 (50)	123 (80)
T2	11 (35)	116 (21)	31 (48)	30 (20)
T3	0 (0)	0 (0)	1 (2)	0 (0)
Overall Cancer Risk				
Low	12 (39)		15 (23)	61 (40)
Intermediate	19 (61)		41 (64)	88 (58)
High	0 (0)		8 (13)	4 (3)
Other Characteristics				
Mean BMI (± SD)	27.2 (3.9)		28.1 (4.6)	28.5 (5.4)
Mean prostate volume, mL (± SD)	45.3 (15.9)		61.0 (25.9)	50.0 (27.0)

Table 2. Interruption Length and Breakdown

	Interruption Time (s)	Pause Time (s)	Reposition Time (s)
Mean	34.2	17.55	40.51
SD	33.79	37.56	51.21
Median	19.68	6	28.5
Minimum	1	1	2
Maximum	601	301	501

Table 3. Maximum Prostate Excursion/Displacement During Beam-On

	Displacement (mm)					
	Left	Right	Superior	Inferior	Anterior	Posterior
Mean	0.5	0.6	1.1	0.9	0.7	1.3
SD	0.6	0.6	0.9	0.9	1.1	0.7
Median	0.5	0.6	1.0	0.9	0.4	1.3
Minimum	-1.1	-1.2	-1.4	-1.2	-4.0	-1.1
Maximum	6.7	6.0	10.7	11.5	11.4	4.5

Table 4. Dosimetric Data

	PTV	Rectum			Bladder		
	$V_{77.4}$ (≥ 98%)	V_{78} (≤5%%)	V_{75} (≤15%)	V_{70} (≤25%)	V_{80} (≤15%)	V_{75} (≤25%)	V_{70} (≤35%)
Mean	98.4%	2.7%	8.2%	14.2%	1.0%	7.5%	10.8%
SD	0.5%	1.6%	3.2%	5.3%	1.7%	4.2%	6.2%
Minimum	98.0%	0.0%	1.3%	3.5%	0.0%	2.5%	3.7%
Maximum	99.9%	6.4%	14.9%	23.0%	7.8%	16.6%	27.0%

Table 5. Patient-Reported Morbidity Comparison (EPIC Scores*)

	Our Study (n=31)			ProtecT (n=545)			
	Score, Mean (SD)	Mean Difference[1] (95% CI)	Clinically Meaningful Decline[2]	Score, Mean (SD)	Mean Difference[1] (95% CI)	Clinically Meaningful Decline[2]	P
Bowel							
Baseline	94.1 (6.6)	--	--	94.8 (6.9)	--	--	--
6 months	90.5 (12.2)	-3.6 (-8.5, 1.3)	Yes	86.3 (16.0)	-8.5 (-10.4, -6.6)	Yes	0.14
12 months	87.8 (14.2)	-6.3 (-11.8, -0.8)	Yes	90.5 (12.2)	-4.3 (-5.8, -2.8)	Yes	0.47
24 months	88.1 (13.7)	-6.0 (-11.4, -0.6)	Yes	89.3 (12.8)	-5.5 (-7.0, -4.0)	Yes	0.86
Urinary							
Baseline	88.9 (10.6)	--	--	93.2 (8.3)	--	--	--
6 months	87.2 (13.3)	-1.7 (-7.7, 4.3)	No	84.7 (13.8)	-8.5 (-10.3, -6.7)	Yes	0.03
12 months	85.2 (14.4)	-3.7 (-10.0, 2.6)	No	91.9 (9.0)	-1.3 (-2.7, 0.1)	No	0.36
24 months	84.3 (14.4)	-4.6 (-10.9, 1.7)	No	91.4 (9.8)	-1.8 (-3.2, -0.4)	No	0.31
Sexual							
Baseline	48.9 (31.8)	--	--	63.6 (23.1)	--	--	--
6 months	41.1 (30.1)	-7.8 (-23.2, 7.6)	No	31.9 (27.1)	-31.7 (-35.8, -27.6)	Yes	<0.01
12 months	36.7 (26.2)	-12.2 (-26.7, 2.3)	No	43.2 (27.6)	-20.4 (-24.5, -16.3)	Yes	<0.01
24 months	41.7 (29.2)	-7.2 (-22.4, 8.0)	No	43.4 (25.9)	-20.2 (-24.1, -16.3)	Yes	<0.01

*Scores range from 0-100 with higher scores indicating better patient reported quality of life.

[1]Change from baseline to follow-up, calculated from within-patient differences.

[2]Defined as mean difference >0.5 SD from baseline value.

Table 6. Patient-Reported Morbidity Comparison between Studies (EPIC Scores*)

EPIC Domain/Study (n)	Pretreatment Mean (SD)	Post-treatment Mean (SD)	Mean Difference (95% CI)	Clinically Meaningful Decline[1]
Bowel/Rectal				
This Study (31)	94.1 (18.1)	83.81 (15.4)	-10.5 (-11.5, -9.5)	Yes
AIM non-NHT (41)	91.8 (19.2)	89.8 (17.6)	-1.9 (-9.0, 5.1)	No
Prost-QA (148)	94.4 (10.8)	78.5 (20.9)	-16.0 (-19.4, -12.5)	Yes
Urinary Irritation				
This Study (31)	88.8 (18.8)	70.6 (20.5)	-18.2 (-19.3, -17.1)	Yes
AIM non-NHT (38)	84.5 (18.0)	80.6 (23.0)	-4.0 (-10.0, 2.1)	No
Prost-QA (148)	86.6 (14.3)	70.1 (20.7)	-16.5 (-19.8, -13.3)	Yes
Urinary Incontinence				
This Study (31)	90.8 (20.3)	86.8 (20.1)	-4.2 (-5.0, -3.4)	No
AIM non-NHT (43)	93.0 (12.5)	86.3 (21.0)	-6.7 (-12.1, -1.3)	Yes
Prost-QA (138)	92.5 (13.1)	84.6 (20.5)	-7.9 (-11.0, -4.8)	Yes
Sexual				
This Study (31)	48.9 (32.5)	41.0 (31.8)	-7.7 (-9.1, -6.3)	No
AIM non-NHT (43)	50.9 (32.1)	50.9 (26.9)	0.0 (-8.6, 8.6)	No
Prost-QA (133)	63.5 (27.8)	51.5 (30.0)	-12.0 (-15.4, -8.5)	No

*Scores range from 0-100 with higher scores indicating better patient reported quality of life.
[1]Defined as mean difference >0.5 SD from baseline value.

Figure 1. Patient Mean Prostate Excursion/Displacement During Beam-On

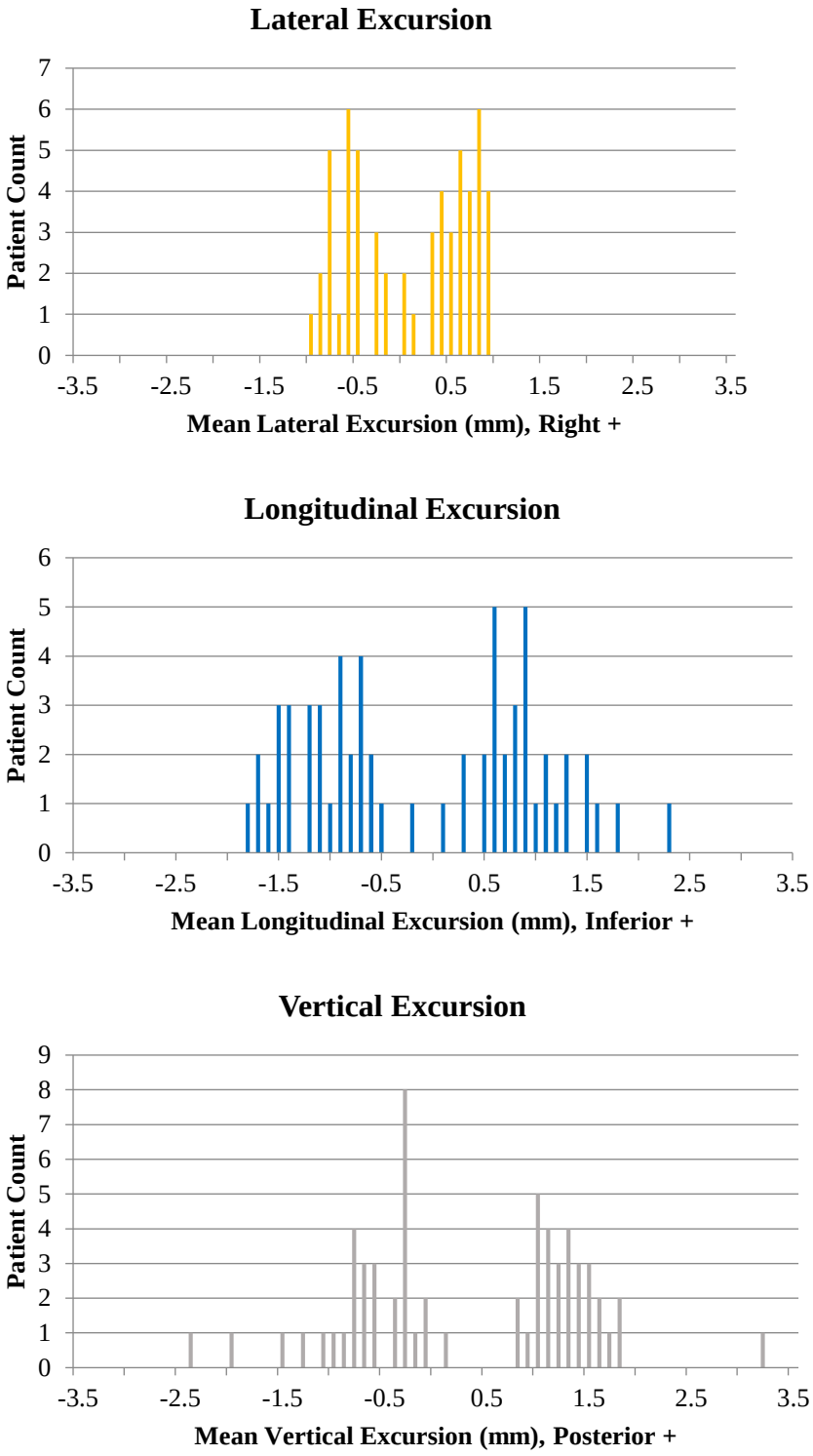
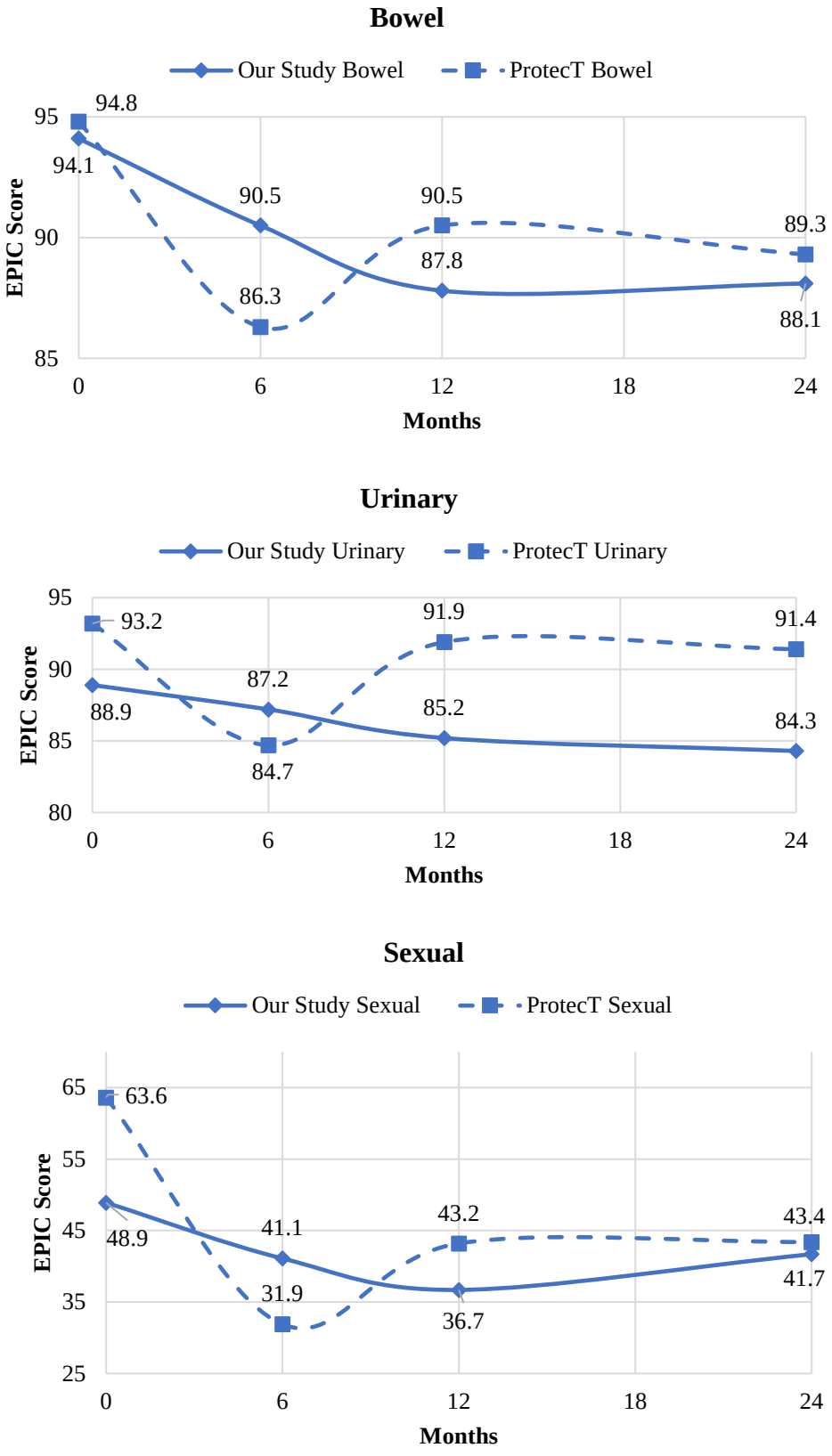


Figure 2. EPIC Scores.



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Original Report

Deep inspiration breath hold with electromagnetic confirmation of chest wall position for adjuvant therapy of left-sided breast cancer: Technique and accuracy

Madeera Kathpal DO [a], Brent Tinnel MD [b], Kelly Sun MS [c], Stephanie Ninneman RN [d], Cynthia Malmer MS [e], Stacie Wendt BA [d], Sheena Buff BS [b], David Valentich BS [b], Marisa Gossweiler DO [f], Dusten Macdonald MD [b,*]

[a]*Department of Radiation Oncology, Fort Belvoir Community Hospital, Fort Belvoir, Virginia*
[b]*Department of Radiation Oncology, Madigan Army Medical Center, Tacoma, Washington*
[c]*F. Edward Hébert School of Medicine, Uniformed Services University of the Health Sciences, Bethesda, Maryland*
[d]*The Geneva Foundation, Tacoma, Washington*
[e]*Northwest Medical Physics Center, Lynwood, Washington*
[f]*Department of Radiology, Madigan Army Medical Center, Tacoma, Washington*

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Abstract

Purpose: With most patients now living long after their breast cancer diagnosis, minimizing long-term side effects of breast cancer treatment, such as reducing late cardiac and pulmonary side effects of radiation therapy (RT), is particularly important. It is now possible to use an electromagnetic tracking system to allow real-time tracking of chest wall (CW) position during the delivery of RT. Here, we report our experience using electromagnetic surface transponders as an added measure of CW position during deep inspiration breath hold (DIBH).

Methods and materials: We conducted a single-institution institutional review board–approved retrospective review of 15 female left-sided breast cancer patients treated between July 2012 and June 2013 with conventional whole breast radiation. We compared daily port films with treatment planning digitally reconstructed radiographs to establish daily setup accuracy, then used Calypso tracings to compare the position of the CW during the daily port film with the position of the CW during that day's treatment to determine the reproducibility of the breath hold position. Finally, we created competing treatment plans not using DIBH and used a paired *t* test to compare mean heart (MH) and left anterior descending (LAD) coronary artery dose between the 2 techniques.

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Conflicts of interest: None.

* Corresponding author. Department of Radiation Oncology, Madigan Army Medical Center, 9040A Jackson Avenue, Tacoma, WA 98431.
E-mail address: dusten.m.macdonald.mil@mail.mil (D. Macdonald).

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Results: Mean total error (inter- and intrafraction) was dominated by interfraction error and was greatest in the longitudinal direction with a mean of 2.13 mm and 2 standard deviations of 8.2 mm. DIBH significantly reduced MH and LAD dose versus free breathing plans (MH, 1.26 Gy vs 2.84 Gy, $P \leq .001$; LAD, 5.49 Gy vs 18.15 Gy, $P \leq .001$).
Conclusions: This study demonstrates that DIBH with electromagnetic confirmation of CW position is feasible, and allows potential improvement in the accurate delivery of adjuvant RT therapy for breast cancer.
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Introduction

Breast cancer remains the most prevalent cancer and a leading cause of cancer death among women.[1] More than 230,000 women will be diagnosed with breast cancer in the United States this year, and many will receive radiation therapy (RT) as part of their initial breast cancer treatment. Adjuvant RT is known to reduce local recurrence, which in turn increases breast cancer–specific survival and overall survival.[2] With most patients now living long after their breast cancer diagnosis, the medical community bears increased responsibility to minimize long-term side effects of treatment for breast cancer. This is particularly true in regard to reducing late cardiac and pulmonary side effects of RT.

In 2013, the *New England Journal of Medicine* published an article reporting on cardiac toxicity incurred in 2168 women treated for breast cancer in Sweden and Denmark between 1958 and 2001. In this group, 963 women suffered major coronary events and 1205 were used as controls. They found that rates of major coronary events increased linearly with mean dose to the heart by a relative rate of 7.4% per Gy, with no apparent low-dose threshold. The risk was noted to start within 5 years of treatment and to continue for at least 20 years.[3]

Electromagnetic beacon transponders (Calypso 4D Localization System, Calypso Medical Technologies, Seattle, WA) are widely used for real-time tracking of prostate motion during RT for prostate cancer. More recently, the US Food and Drug Administration has approved the use of electromagnetic beacon transponders designed to be placed on the body surface during RT. Therefore, it is now possible to use an electromagnetic tracking system to allow real-time tracking of chest wall (CW) position during the delivery of RT. We recognized this benefit for patients with left-sided breast cancers (LBC) and developed a protocol using electromagnetic surface transponders to track CW position during deep inspiration breath hold (DIBH). Our standard procedure included daily port films as the primary method of verifying CW position.

In the present study, we review the entire treatment course for 15 breast cancer patients treated with this technique. By using an auto-match function verified by visual confirmation to compare daily port films with treatment planning digitally reconstructed radiographs (DRRs), we established daily setup accuracy. We then used Calypso tracings to compare the position of the CW during the daily port film versus that day's treatment to determine the reproducibility of the breath hold (BH) position. Finally, we created competing treatment plans, not using DIBH, to establish the benefit in reduction of dose to the heart with this technique.

Methods and materials

Patient population

We conducted a single-institution institutional review board–approved retrospective review of 15 female LBC cancer patients treated between July 2012 and June 2013 with conventional whole breast radiation. Candidates for this study were patients with noninvasive or invasive LBC who were able to comfortably hold their breath for about 20 seconds at the time of initial simulation.

Patients were between 42 and 70 years of age, with a median age of 55 years. Most of the patients had negative nodal status, were estrogen receptor positive, and received adjuvant systemic therapy (Table 1). All patients were treated with 6-MV photons through opposed tangents to a dose of 50 Gy in 25 fractions followed by a lumpectomy cavity boost. One patient had a supraclavicular field treated, also in the DIBH position. One patient was treated with a couch kick, which required minor adjustments in interpreting the Calypso reports.

Simulation

Patients were placed supine on a breast board on the computed tomography (CT) scanner table. The physician then outlined field borders and a marker was placed on the sternum about halfway between the superior and inferior borders of the marked field, which would eventually be the BH mark. Lateral level marks as delineated by the external lasers in this position were also marked.

A free breathing (FB) CT simulation scan was performed to determine if the DIBH technique was required. The treating physicians examined the FB CT scan and approximated how much heart would be in the field using standard tangents. If the treating physician determined the patient would benefit from DIBH during treatment, additional steps during the simulation were performed, as outlined in the following section.

Table 1 Patient characteristics

Characteristic	
Age	
Range	42-70
Median	55
Pathologic stage	
0	8
IA	2
IB	0
IIA	4
IIB	1
Nodal status	
Negative	12
Positive	3
Tumor size (cm)	
0-0.5	4
>0.5-1.0	4
>1.0-2.0	4
>2.0	3
Receptor status	
Estrogen receptor positive	14
Her-2 receptor positive	2
Triple negative	1
Hormonal therapy	
Yes	11
No	4
Adjuvant chemotherapy	
Yes	4
No	11

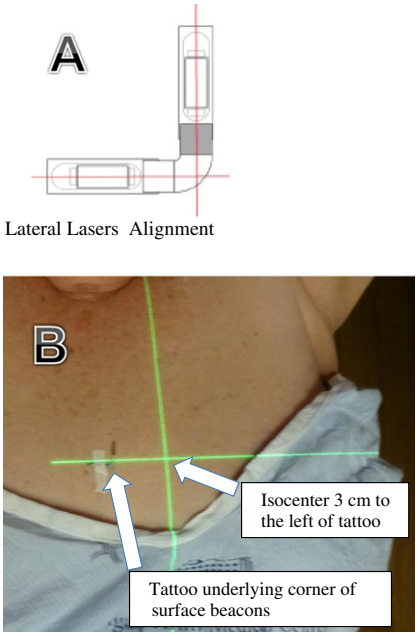

Figure 1 (A) Laser alignment with beacons placed on the sternum for breast treatment on the treatment table. (B) Photograph demonstrates position of the beacons in relation to breath hold tattoo.

DIBH technique

After ensuring the patient was properly aligned and straight on the breast board, the patient was instructed to perform a DIBH. Longitudinal (ie, craniocaudal) movement of the BH mark was observed, measured, and recorded. The patient was coached and asked to repeat the DIBH until the longitudinal movement of the BH mark was reproducible. The external Calypso beacon pair was then placed on the BH mark and another CT scan was performed with the patient undertaking DIBH. After the physician approved the scans and technique, permanent tattoos replaced the leveling and BH marks and an additional straightening mark was placed on the sternum inferior to the BH tattoo.

Treatment planning

Both FB and DIBH CT scans were transferred to the treatment planning system. All planning was performed on the DIBH CT scan using the Pinnacle treatment planning system. All patients were treated with opposed tangents with the least amount of tangent segments possible to minimize time required for the DIBH technique. Physical wedges were not used; however, enhanced dynamic wedges were acceptable in lieu of segments if the BH time did not exceed approximately 20 seconds per field. The lasers were localized at the BH tattoo. The isocenter was placed 2 cm posterior and 3 cm lateral to the BH tattoo.

Each Calypso beacon was assigned as a point in Pinnacle, which provided the beacon coordinates for entry into the Calypso System. The medial beacon was identified in the Calypso system as the left mid-base with a medium transponder frequency. The black ringed beacon pointing superiorly was the apex beacon and had the lowest frequency. The isocenter and beacon coordinates from the Pinnacle treatment plan had the following tolerances: lateral, 3.0 cm; longitudinal, 4.0 cm; vertical, 5.0 cm; geometric residual, 0.3 cm; and rotational alignment, 30°.

Treatment setup

The patient was set up on a breast board as at the time of simulation. While FB, the patient was leveled and straightened using external lasers and the leveling marks, BH mark, and the anterior straightening mark. The patient was then directed to perform a DIBH. The therapists observed the subsequent location of the BH tattoo to confirm the DIBH was of a similar magnitude to that during simulation. The patient then performed another DIBH and was shifted so the light field cross-hairs aligned with the BH mark. The therapists placed the beacon pair on the patient and verified that the light field cross-hairs bisected the beacons during DIBH (Fig 1A). Also, during

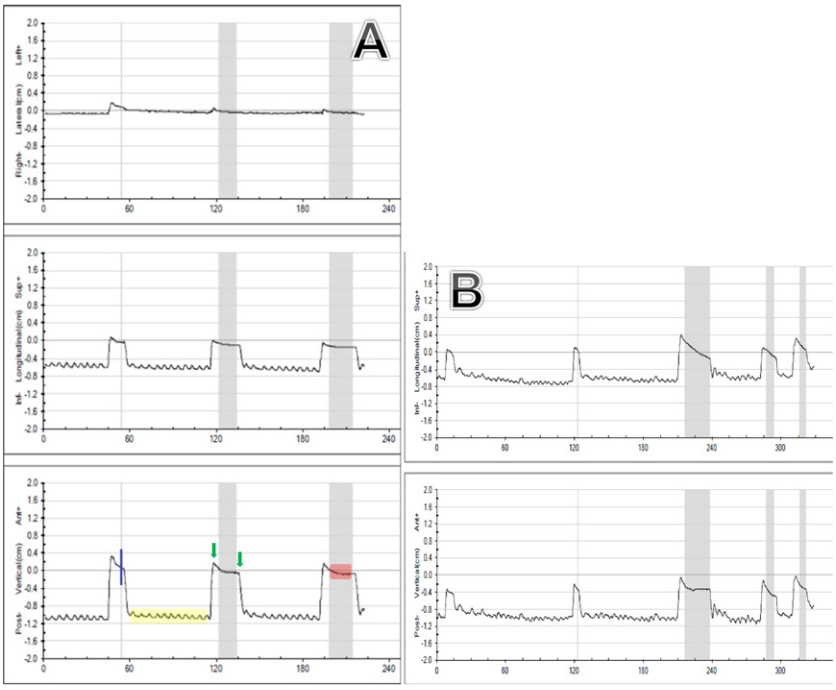

Figure 2 (A) Transponder tracking report showing chest wall position in all 3 axes at the time of daily port film (vertical blue line), free breathing (yellow highlight), deep inspiration breath hold (mean distance between maximum and minimum values [green arrows]), and beam-on time (red highlight/shaded area). (B) Example of a transponder tracking report with a split-beam during the second tangent. Ant, anterior; inf, inferior; post, posterior; sup, superior.

DIBH, source-to-skin distance was set to 98 cm at the BH mark. Finally, a standard lateral shift of 3 cm (patient moved right, isocenter moved left) was applied (Fig 1B). The therapists then had the patient perform a final preparation DIBH, so the Calypso unit could localize and begin to track the 2 beacons.

Treatment

From outside the treatment room, therapists requested the patient take a DIBH, and a single-exposure port film was acquired. If this was unsatisfactory, the patient was

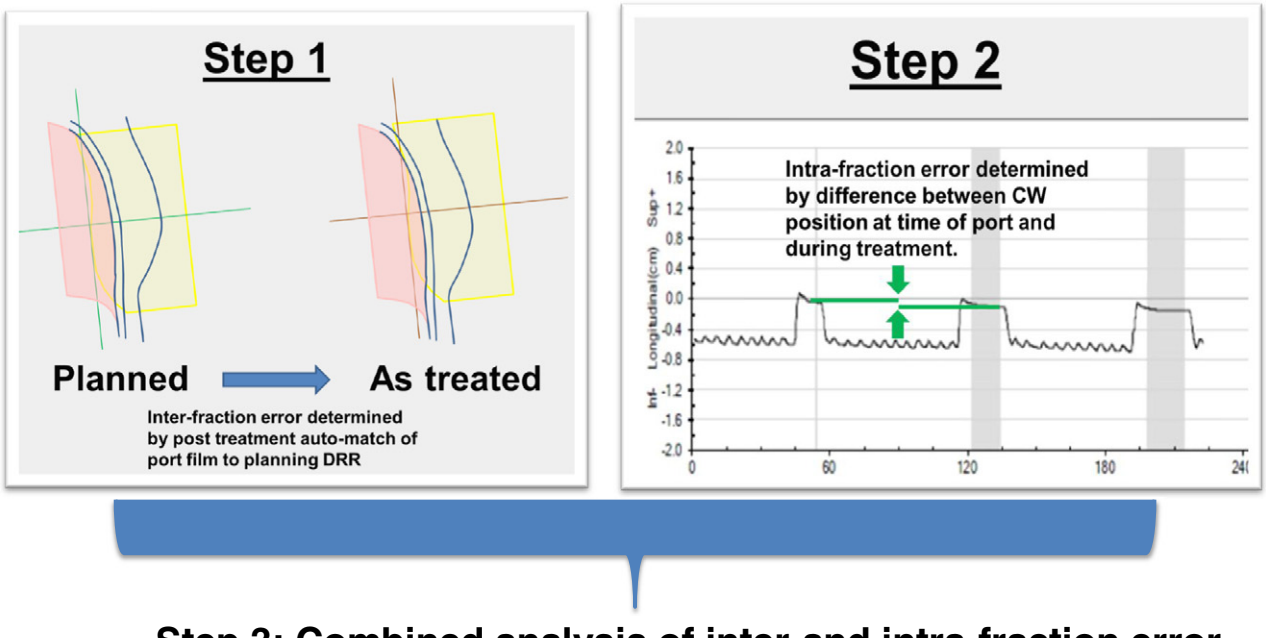

Figure 3 Depiction of measurements used to determine the interfraction error (step 1), the intrafraction motion (step 2), and the necessary planning treatment volume margin (step 3). CW, chest wall; DRR, digitally reconstructed radiograph.

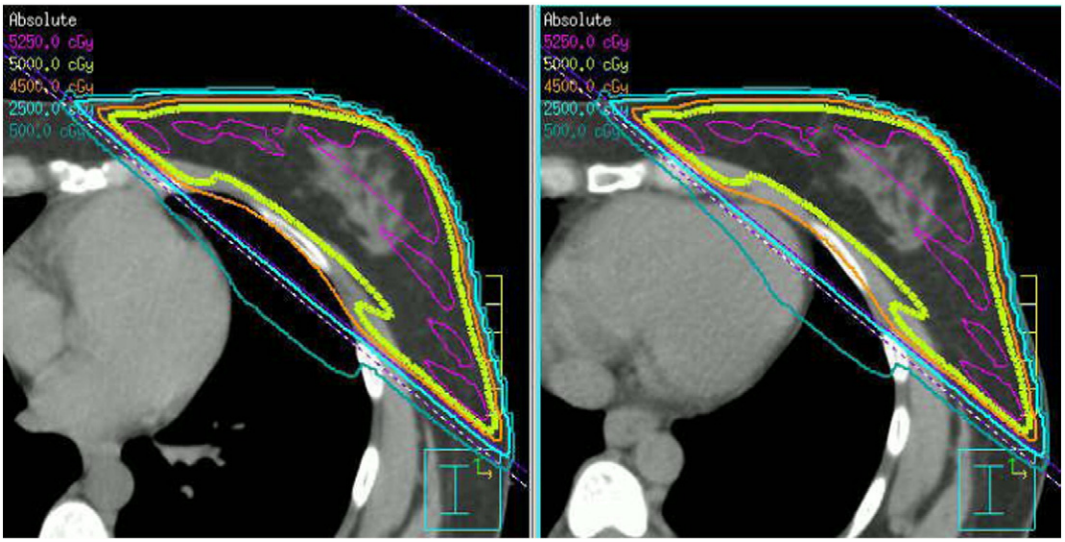

Figure 4 Deep inspiration breath hold computed tomography scan with isodose lines showing sparing of heart (left); free breathing computed tomography scan at same slice as deep inspiration breath hold scan showing inclusion of heart within the tangent (right).

repositioned by coaching BH technique (if Calypso tracings indicated a difference between setup BH and port film BH) or table shift until a satisfactory port film was taken.

The average number of ports taken per day of treatment was 1.5, with the majority of patients having either 1 or 2 ports taken per day; 98.4% of these images were closed-field ports, so did not contribute a significant additional heart dose. Additional dose to lung and soft tissue within the treated field was estimated to be within 1% of the planned treatment dose.

During treatment, therapists monitored the Calypso tracings and stopped the beam, if necessary, to constrain beam-on CW position to within about 2 mm of the port film CW position. Because beacons track the relative position of the chest wall (ie, the difference in CW position between the time of port film and the time of treatment), small differences in beacon placement on the CW from day to day were not considered a source of error. Therefore these differences, which are thought to be in the range of <1 mm, were not measured.

Retrospective measurement of port film alignment in comparison to DRRs

Each patient's treatment planning DRR was auto-matched (with visual confirmation of accuracy) to each day's port film. The positional difference between the actual port and the now positionally optimized port was recorded in 3 dimensions along the lateral, vertical, and longitudinal axes. Auto-match parameters were set so the area of interest was in line with the outer corners of the planned field edge before the auto-match was conducted. The auto-match was performed twice for each port film. Using these data, the mean initial positioning error was calculated to represent interfraction motion. Although the beacons are radiopaque, they typically do not appear in the port films because they are positioned either outside, or at the border of, the imaged field.

Mathematical recreation of the 3-dimensional position of the target tissues

Maximum intrafraction excursions were determined by examining Calypso tracings that portray the position of surface beacons through the port film and treatment (Fig 2). High, low, and best-fit positions of the CW were recorded for each daily port film and treatment beams. The high and low points represent the largest and smallest excursions, respectively, superiorly, anteriorly, and to the left during treatment along the longitudinal, vertical, and lateral axes. The best-fit measurement represents the position the patient spent the most time in during beam-on time. This position was compared with that during port filming from the same day; this difference was recorded as the intrafraction motion of the CW for that beam. The intrafraction motion from each beam was then combined with the auto-shift measurements, which aligned that day's port film with the treatment plan DRR to determine the total precision of the patients' 3-dimensional position in relation to the planned treatment (Fig 3).

Mean heart and left anterior descending coronary artery dose

The heart was contoured in every patient according to Radiation Therapy Oncology Group guidelines. The left anterior descending (LAD) coronary artery was contoured superiorly from the beginning of the left atrium, down to

Table 2 Mean interfraction positional error based on comparison between daily port film and digitally reconstructed radiograph of the deep inspiration breath hold simulation computed tomography, mean intrafraction motion (mm) with 2 SD, and mean total precision (mm) with 2 SD

	Longitudinal	Vertical	Lateral	
Interfractional error	2.16 inferior	0.61 posterior	0.42 left	Mean
	7.9	4.4	3.8	2 SD
Intrafractional error	0.10 superior	0.11 anterior	0.09 left	Mean
	3.1	2.3	2.5	2 SD
Total precision	2.13 superior	0.47 posterior	0.51 left	Mean
	8.2	4.9	4.6	2 SD

SD, standard deviation.

the apex inferiorly. In addition to the DIBH treatment plan, a second plan was created using the FB CT scan and the same anatomical beam entry and exit points as the DIBH plan (Fig 4). The FB and DIBH treatment plans' heart and LAD mean doses were calculated and recorded from each dose-volume histogram. Three FB scans were unable to be analyzed because of incomplete heart visualization. We used a paired *t* test to compare mean heart (MH) and LAD dose with and without DIBH and CW excursion during DIBH to that during beam-on.

Results

The mean number of treatment BHs per fraction was 2.3; 23% of treatment beams were interrupted to adjust for suboptimal BH or CW position. The interfraction positioning error data are presented in Table 2 as mean values in the vertical (anteroposterior), longitudinal (superior/inferior), and lateral (left/right) directions. The mean positional error of the daily port films by auto-match comparison to the DRR of the DIBH simulation CT was 0.61 mm posteriorly, 2.16 mm inferiorly, and 0.42 mm to the left. The difference from the Calypso beacon position during treatment to the position at the time of port film, or the mean intrafraction motion (Table 2), was 0.11 mm anteriorly, 0.10 mm superiorly, and 0.09 mm to the left. The greatest variability in intrafraction motion was in the longitudinal direction; in that axis, 95% of treatments (2 standard deviations [SD]) fell within 3.1 mm of the port film position. The total precision of the study technique was determined by combining the 2 previous measures for each treatment. The mean total precision (Table 2) was 0.47 mm posteriorly, 2.13 mm superiorly, and 0.51 mm to the left.

We compared DIBH CW position during the entire BH (plateau) to position during beam-on (Table 3). The mean (SD) CW motion during the entire DIBH was 4.2 (2.8) mm, 5.0 (4.0) mm, and 2.5 (2.3) mm in the vertical, longitudinal, and lateral axes, respectively. Overall, this was significantly larger than the CW motion during beam-on of 1.3 (0.9) mm, 1.7 (1.4) mm, and 1.1 (1.2) mm in the vertical, longitudinal, and lateral axes, respectively ($P < .001$ in all dimensions).

Table 4 shows the dosimetric comparison of MH dose and mean LAD dose between the FB and BH simulation CT scans. DIBH significantly reduced MH and LAD dose versus FB plans (MH, 1.26 ± 0.51 Gy vs 2.84 ± 1.55 Gy, $P \leq .001$; LAD, 5.49 ± 4.02 Gy vs 18.15 ± 8.78 Gy, $P \leq .001$).

Discussion

Our study shows electromagnetic confirmation of CW position is technically feasible, allows for verification of BH reproducibility to within 3.1 mm (2SD) in 95% of fractions, and allows therapists to constrain beam-on time to the most reproducible and stable portion of each BH. With our technique, DIBH during irradiation of LBC patients reduced the MH and LAD dose by at least 50%.

The importance of minimizing dose to the heart during adjuvant RT for LBC has become increasingly clear as this issue has been studied over the past decade. For example, long-term mortality from heart disease after RT was studied using the US Surveillance, Epidemiology, and End Results cancer registry. Women with left-sided tumors were compared with those with right-sided tumors. For women treated in the 1970s and 1980s, cardiac mortality 10 years or longer after radiation treatment was higher in women with left-sided tumors.[4] Similar findings were

Table 3 Mean CW excursion ±1 SD during entire DIBH and during beam-on ($P < .001$ in all dimensions)

	Lateral (LR)	Longitudinal (SI)	Vertical (AP)
CW excursion during DIBH	2.5 ± 2.3	5.0 ± 4.0	4.2 ± 2.8
CW excursion during beam-on	1.1 ± 1.2	1.7 ± 1.4	1.3 ± 0.9

AP, anteroposterior; CW, chest wall; DIBH, deep inspiration breath hold; LR, left/right; SD, standard deviation; SI, superoinferior.

Table 4 Mean heart and LAD dose between FB and BH scans (Gy)

	Heart		LAD	
	FB	BH	FB	BH
Mean	2.84	1.26	18.15	5.49
2 SD	3.10	1.03	17.57	8.04
Range	1.43-6.79	0.60-2.16	3.12-35.16	3.10-10.93

$P < .001$ for both heart and LAD comparisons.
BH, breath hold; FB, free breathing; LAD, left anterior descending coronary artery; SD, standard deviation.

seen in 961 patients with stage I or II breast cancer treated with adjuvant RT at the University of Pennsylvania between 1977 and 1994. At 20 years after treatment, an increased risk of cardiac mortality was seen in patients treated for left versus right breast cancers. Diagnosis of chest pain, coronary artery disease, and myocardial infarction was also statistically higher in left-sided patients.[5]

A group from Canada specifically studied mortality from myocardial infarction after RT.[6,7] An increased risk of fatal myocardial infarction was found in women with LBC compared to right-sided cancers. This difference was most evident in women younger than 60 years of age. Internal mammary chain irradiation, use of adjuvant chemotherapy with adjuvant radiation and smoking have all been shown to increase risk of cardiovascular disease in 10-year survivors of breast cancer.[8]

The physiologic basis for the increased risk of cardiac mortality following RT for breast cancer has been proposed to be radiation-associated coronary damage. A group from the University of Pennsylvania demonstrated an increase in single-photon emission CT myocardial perfusion stress testing or transthoracic stress echocardiogram abnormalities a median of 15 years after treatment. Nearly half of the LBC patients with these abnormalities underwent cardiac catheterization with nearly all showing coronary stenosis involving the LAD artery.[9]

Certainly, many groups have studied the use of DIBH to assist in limiting heart dose during adjuvant RT for breast cancer. For example, Giraud et al reported on the benefits of using the BH technique in the treatment of patients with breast cancer. They found a significant reduction in volume of lung and heart treated when using BH versus FB during treatment. They also found a reduction in maximum dose to the contralateral breast. There was no difference in early or late toxicity between the 2 treatment modalities.[10]

To our knowledge, we are the first to report a careful study of the use of electromagnetic transponders to track CW position when using DIBH technique. Our study shows that the CW is not necessarily stable during DIBH. Tracking CW motion allowed our therapists to limit beam-on time to the most stable portions of the BH.

We were able to couple retrospective analysis of daily port films with Calypso tracings, which allowed us to make conclusions regarding the accuracy of this treatment technique. The interfraction error we determined from the port films dominated these measurements, with 2 SD for longitudinal errors of nearly 8 mm. On the other hand, intrafraction motion, or the comparison of CW position at the time of port film to that at the time of beam-on was shown to be small, with 2 SD for longitudinal errors of 3.1 mm. It is apparent that often these 2 errors occurred in opposite directions, such that the average of the daily combination of interfraction and intrafraction error was very similar to the interfraction error alone.

There is a small added cost to this method of verification. Using daily port films adds 20 additional port film charges in addition to the 5 that would be billed during a course of treatment verified with weekly ports alone. With the Centers for Medicare & Medicaid Services reporting the 2015B national payment amount for radiology port films in a hospital at $10.78, this equated to an average additional cost of $215.60 per course of treatment. At present, there is no additional charge for using Calypso tracking during treatment.

Finally, our dosimetric comparison demonstrated that in this carefully selected group, DIBH technique does reduce mean dose to the heart as well as dose to the LAD artery.

Our study does suffer from significant limitations, with the primary limitation being a small sample size. Other limitations include the inaccuracies inherent in using an auto-match algorithm to compare port films to DRRs and that measurements of CW position from Calypso tracings were obtained manually. However, we feel that the use of an auto-match algorithm allowed us to objectively compare films, and the errors potentially introduced by making manual measurements from Calypso tracings should be very small.

In conclusion, we have demonstrated that DIBH with electromagnetic confirmation of CW position is feasible and allows potential improvement in the accurate delivery of adjuvant RT for LBC.

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Appendix 3
Abstract: Anorectal Angle and Bowel Toxicity Following Radiation Therapy for Prostate Cancer. *

** Mitchell D, Tinnel B, Brand T, Huang R, Gossweiler M, Ninneman S, Wendt S, Macdonald D. (17-19 March 2016). Anorectal Angle and Bowel Toxicity Following Radiation Therapy for Prostate Cancer. Poster presented the ACRO 2016 Annual Meeting, Orlando, FL.*

PURPOSE/OBJECTIVES: Some elements of bowel toxicity following radiation therapy (XRT) for prostate cancer – such as urgency, frequency, or fecal leakage – may be related to anal canal geometry and musculature. In a hypothesis-generating study presented at the 2013 ASTRO/RSNA Cancer Imaging and Radiation Therapy Symposium we reported a statistically significant correlation between larger anorectal angle (ARA) and self-reported bowel toxicity in a sample of 10 patients. We have since continued to accumulate data and herein report our evaluation of this potential association with a larger cohort.

MATERIALS/METHODS: We studied 28 consecutive patients with low-to-intermediate risk prostate cancer treated on a prospective clinical study with definitive intensity-modulated radiation therapy (IMRT). Patients completed the EPIC quality of life questionnaire at baseline and at four post-treatment time points. We averaged EPIC bowel scores from the final day of treatment and 1 month post-treatment to get an acute toxicity score, and averaged scores at 4 and 10 months post-treatment to get a chronic toxicity score. We tabulated EPIC scores so that a score of 100 reflected a "perfect score" (no toxicity). ARA was measured on the mid-sagittal slice of treatment planning CT scans as the angle formed by the intersection of the central axes of the lower rectum and anal canal. Patients were divided by the mean ARA (104°) into two groups, "large ARA" and "small ARA." We used a two-tailed t-test to compare mean EPIC scores of the two groups at each time point at alpha level 0.05.

RESULTS: ARA ranged from 86° to 131.5°, with both mean and median values of 104°. There was no statistically significant difference between small and large ARA groups in baseline EPIC bowel scores, not in acute or chronic toxicity scores. Mean EPIC scores and p values for each comparison are shown in Table 1.

CONCLUSIONS: In this group of 28 patients there appears to be no association between a larger ARA and increased bowel toxicity following XRT for prostate cancer. There was some evidence of increased baseline bowel symptoms in men with larger ARA which was not statistically significant.

Table 1: Mean EPIC bowel scores +/- standard deviation for each group at each time point.

	Baseline	Acute	Chronic
Small ARA	95.7 ± 5.1	87.3 ± 11.1	90.1 ± 14.5
Large ARA	91.8 ± 7.0	84.2 ± 14.2	88.8 ± 10.4
p value	0.098	0.518	0.808

Appendix 4

Abstract: Change in Practice Patterns and Increasing Use of Modern Technology for Palliative Treatments at a Military Hospital. *

** Premo C, Tinnel B, Collins M, Ninneman S, Kathpal M, Buff S, Ahrmendi J, Stanke A, Valentich D, Macdonald D. (29 November – 4 December 2015). Change in practice patterns and increasing use of modern technology for palliative treatments at a military hospital. Poster to be presented at the 101st Scientific Assembly and Annual Meeting of the Radiological Society of North America (RSNA), Chicago, IL.*

** Premo C, Tinnel B, Collins M, Ninneman S, Kathpal M, Buff S, Ahrmendi J, Stanke A, Valentich D, Macdonald D. (29 November – 4 December 2015). Change in practice patterns and increasing use of modern technology for palliative treatments at a military hospital. Poster presented Madigan Army Medical Center's 2016 Annual Research Day, Tacoma, WA.*

PURPOSE/OBJECTIVES: A wide range of doses, fractionation schemes, and techniques can be employed for palliative treatments. Randomized trials and recent ASTRO guidelines support the use of single fraction or hypo-fractionated regimens, particularly for painful bone metastasis. With comparable efficacy, regimens of 1-5 fractions are more cost effective and convenient for patients and caregivers. The choice of total dose, fractions, and technique may be influenced by financial factors including insurance coverage. In military hospitals these decisions are determined on a case by case basis with different financial considerations than those faced in non-military institutions. Herein we examine the change in practice patterns for palliative treatment over the course of 8 years at a military hospital.

MATERIALS/METHODS: Patients treated with palliative intent from June 2006 – December 2007 and from January 2013 - June 2014 were retrospectively reviewed in this IRB-approved study. This included 80 and 69 patients, respectively. Total dose, dose per fraction, number of fractions, number of sites treated, technique, and number of single fraction treatments were compared between the two groups, using a paired t-test for continuous variables and 95% confidence intervals (95% CI) for categorical variables. We excluded whole brain treatments and non-solid tumor treatments which led to the inclusion of 100 and 129 treated sites, respectively.

RESULTS: Between 2006-2007 (group 1) and 2013-2014 (group 2), there was a significant increase in the average dose per fraction, with mean dose of 328 cGy for group 1 vs 504 cGy for group 2 (mean difference 175 cGy, $p < 0.0001$). The mean total dose per site and mean number of fractions decreased over time. The mean total dose/site was 2858 cGy in group 1 and 2182 cGy in group 2 ($p < 0.0001$). There was a large difference in the use of single fraction treatments between the two groups as well, 8% in group 1 (95% CI 4% to 15%) and 34% in group 2 (95% CI 26% to 43%). The use of IMRT/VMAT/Arc increased from 0% in group 1 (95% CI 0% to 4%) to 21% in group 2 (95% CI 15% to 29%). The mean number of sites treated per patient was not significantly different (2.3 and 2.6 in groups 1 and 2, respectively, $p = 0.3$).

CONCLUSIONS: We found a significant increase in the use of shorter palliative treatments, higher doses per fraction, single fraction treatments, and use of advanced technologies over the time range studied. These changes represent the implementation of modern techniques when deemed necessary and beneficial to patients, in a setting less constrained by insurance billing practices. In addition, the increase in single fraction treatments represents a more cost effective use of palliative radiation which follows consensus guidelines supported by randomized evidence.

Appendix 5
Abstract: Disruptive Innovation in Proton Therapy. *

** Macdonald D, Ninneman S, Tinnel B. (27 February 2015). Disruptive innovation in proton therapy. Oral presentation given at the 54th Annual Conference of the Particle Therapy Co-Operative Group (PTCOG), San Diego, CA.*

BACKGROUND: The theory of disruptive innovation has been used to describe the process by which large incumbent businesses are overtaken by businesses which initially produce a simpler, cheaper, and inferior product, but gain a foothold with less-demanding customers and are then propelled along a unique improvement trajectory. We examined whether applying proton therapy in the palliative setting could provide opportunities for improvement in patient care through phenomena related to disruptive innovation.

METHODS: We contrasted low-to-moderate dose palliative proton therapy with definitive high-dose proton therapy in relation to hallmarks of disruptive innovation as described by Christensen[1]:

Hallmark 1 - a situation in which there is a limit in the ability to absorb new technology

Hallmark 2 - a population of customers for whom the technology has outpaced their ability to use it

Hallmark 3 - the opportunity for a simpler product to be introduced to a larger, less-demanding customer base followed by a rapid improvement cycle.

RESULTS: We found good correlation between palliative proton therapy and the above listed elements of disruptive innovation including (Hallmark 1) logistic, economic, and clinical research hurdles which limit the widespread use of proton therapy as currently delivered. (Hallmark 2) High dose proton therapy is viewed as useful mainly for either improving high dose conformality or reducing low dose spillage, overshooting the needs of palliative patients in both these areas. (Hallmark 3) There is an opportunity for lower-dose palliative proton therapy to succeed with simplified dosimetry and delivery techniques particularly applicable to spot-scanning proton therapy systems, with short palliative treatment courses fit into otherwise unused treatment slots, decreasing the true cost of such treatment. Finally, and most importantly (also Hallmark 3), palliative proton therapy would allow for a rapid improvement cycle secondary to a short clinical trial completion time and important research opportunities suited to this population such as proton RBE modulation, spatial fractionation, and immunomodulatory effects.

CONCLUSIONS: It may be possible to improve patient care through phenomena related to disruptive innovation if we develop simplified planning and quality assurance methods for lower-dose palliative proton therapy with treatment fit into patient flow gaps at proton therapy centers. Disruptive innovation theory predicts that offering this treatment at prices low enough to maximize its use could lead to increased efficacy of proton therapy along previously undervalued axes, with eventual recoupment of initial investment.

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Appendix 6
Abstract: Prostate Cancer Radiation Therapy with Reduced Planning Target Volume (PTV) Margins. *

** Sun K, Kathpal M, Tinnel B, Brand T, Ninneman S, Hughs G, Halligan J, Brown M, Brooks J, Macdonald D. (26 February 2015). Prostate cancer radiation therapy with reduced planning target volume (PTV) margins. Poster presented at the 2015 Genitourinary Cancers Symposium, Orlando, FL.*

** Sun K, Kathpal M, Tinnel B, Brand T, Ninneman S, Hughs G, Halligan J, Brown M, Brooks J, Macdonald D. (2015, April). Prostate cancer radiation therapy with reduced planning target volume (PTV) margins. Poster presented at Madigan Army Medical Center's Annual Research Day, Tacoma, WA.*

BACKGROUND: Electromagnetic tracking of the prostate during definitive radiation therapy for prostate cancer allows decreased PTV margins which may reduce dose to nearby tissues. Sandler, et al. reported a reduction in patient-reported acute morbidity with this strategy. We conducted a similar prospective study and compare our results with Sandler's Assessing Impact of Margin Reduction (AIM) study and with a group treated with radiation therapy without reduced PTV margins from the Sanda, et al. PROST-QA cohort.[2]

METHODS: 25 patients with low-to-intermediate risk prostate cancer were treated on an IRB-approved prospective study with definitive intensity-modulated radiation therapy with 3 mm circumferential PTV margins and daily electromagnetic localization. An EPIC quality of life questionnaire was completed prior to treatment and at the last treatment. Using data from the referenced publications, we performed a two-tailed t-test to compare EPIC scores from our cohort with the AIM and PROST-QA cohorts treated with external beam radiation therapy alone.

RESULTS: Table 1 lists mean pre- and post-treatment EPIC scores and the differences between them.

Table 1: Mean EPIC Score Comparison.

EPIC Domain/Study (n)	Mean (SD)		Mean Difference (95% CI)	P-value in relation to this study
	Pretreatment	Post-treatment		
Bowel/Rectal				
This study (25)	95 (7)	83 (17)	12 (5, 19)	
AIM (41)	92 (19)	90 (18)	2 (-5, 9)	0.07
Prost-QA (148)	94 (11)	79 (21)	16 (13, 19)	0.32
Urinary Irritation				
This study (25)	90 (10)	69 (22)	21 (12, 29)	
AIM (38)	85 (18)	81 (23)	4 (-2, 10)	0.002
Prost-QA (148)	87(14)	70 (21)	17 (13, 20)	0.36
Urinary Incontinence				
This study (25)	90 (18)	86 (22)	4 (-2, 9)	
AIM (43)	93 (13)	86 (21)	7 (1, 12)	0.47
Prost-QA (138)	93 (13)	85 (21)	8 (5, 11)	0.28
Sexual				
This study (25)	58 (35)	42 (34)	17 (6, 28)	0.28
AIM (43)	51 (32)	51 (27)	0 (-9, 9)	0.02
Prost-QA (133)	64 (28)	52 (30)	12 (9, 15)	

CONCLUSIONS: Our patients fared similarly to the PROST-QA cohort, but had a significantly greater mean decrement in the urinary irritation and sexual domains, and a trend toward a greater mean decrement in the bowel/rectal domain, in comparison to the AIM cohort.

APPENDIX 7

Abstract: Reduced Planning Target Volume (PTV) Margins With Real-Time Electromagnetic Tracking during Definitive Radiation Therapy for Prostate Cancer.*

** Sun K, Brand T, Hughs G, Halligan J, Tinnel B, Macdonald D. (26 October 2014). Reduced planning target volume (PTV) margins with real-time electromagnetic tracking during definitive radiation therapy for prostate cancer. Poster presented at the Western Section American Urology Association, Maui, HI.*

PURPOSE: Definitive radiation therapy for prostate cancer may lead to gastrointestinal (GI) and genitourinary (GU) toxicities. Real-time electromagnetic tracking of the prostate minimizes intra-fraction prostate motion and allows decreased PTV margins, which should decrease the dose administered to the bowel and bladder near the prostate. We evaluated the feasibility and clinical outcome of this strategy, and report preliminary results here.

MATERIALS AND METHODS: 24 patients with low-to-intermediate risk prostate cancer were treated on a prospective study with definitive intensity-modulated radiation therapy (IMRT) using an electromagnetic localization system. 3mm PTV margins were used, with 2mm electromagnetic tracking limits. Timing metrics were recorded for each treatment. Patients completed the EPIC quality of life questionnaire prior to treatment, at the last treatment, and at regular follow-up intervals. During clinical follow-up at the same time points, toxicity scores were assigned by a radiation oncologist using the NCI Common Toxicity Criteria.

RESULTS: The median follow-up period was 24 months (range, 3-59 months), during which no patient experienced biochemical failure (Phoenix definition). Mean total daily treatment time was 10.0 minutes (range 7.1 to 15.3 minutes). 79% of patients experienced acute side effects and 54% experienced late side effects – but, in general, side effects were mild. 1 patient (4%) experienced an acute grade 3 GU side effect (urinary retention requiring TURP) and there were no acute grade 3 GI side effects. 13% of patients experienced late grade 2 GU side effects and 13% late grade 2 GI side effects, with no late grade 3 or 4 side effects reported. Mean EPIC scores for bowel, urinary, and sexual function areas at three time points are presented in Table 1 below.

Table 1: Mean EPIC Scores (% of best possible score)

	Bowel	Urinary	Sexual Function
Baseline	93.0 ± 6.9	89.3 ± 10.7	49.7 ± 28.8
Final XRT	79.5 ± 15.1	72.9 ± 19.2	37.3 ± 29.3
4 Months Post Treatment	88.4 ± 32.4	86.4 ± 16.2	35.0 ± 13.9

CONCLUSIONS: Definitive radiation therapy for prostate cancer with reduced PTV margins was clinically feasible and very well tolerated. Serial EPIC scores demonstrate mild changes in bowel, urinary and sexual function areas. This data will be useful in counseling patients regarding treatment options for low-to-intermediate risk prostate cancer.

APPENDIX 8

Abstract: Deep Inspiration Breath Hold (DIBH) With Electromagnetic Surface Transponder Confirmation of Chest Wall (CW) Position During Radiation for Left Breast Cancer.*

** Kathpal M, Sun K, Malmer C, Ninneman S, Wendt S, Hughs G, Macdonald D, Tinnel B. (4 September 2014). Deep inspiration breath hold (DIBH) with electromagnetic transponder confirmation of chest wall position for radiation therapy of left breast cancer. Poster presented at The American Society of Clinical Oncology/Breast Cancer Symposium, San Francisco, CA.*

** Kathpal M, Tinnel B, Malmer C, Ninneman S, Wendt S, Hughs G, Gossweiler M, Valentich D, Buff S, Macdonald D. (2015, April). Deep inspiration breath hold (DIBH) with electromagnetic surface transponder confirmation of chest wall position for adjuvant therapy of left breast cancer. Oral presentation given at Madigan Army Medical Center's Annual Research Day, Tacoma, WA.*

BACKGROUND: DIBH during radiation of left breast cancers reduces heart dose, potentially reducing late cardiac ischemic events, but requires a treatment CW position significantly different from a free-breathing (FB) position. We sought to improve the accuracy of radiation therapy during DIBH by using electromagnetic surface transponders to track the position of the CW during treatment. We examined the benefit of this technique in reducing dose to the heart and consistently reproducing the DIBH position. We also evaluated the difference between FB and DIBH CW position and compared CW movement within the plateau of each DIBH to within beam-on time.

METHODS: 15 patients participated in this IRB-approved study. Patients were planned and treated using DIBH. We fused treatment-position FB CT scans to DIBH scans to compare mean heart (MH) and left anterior descending coronary artery (LAD) dose. We used surface transponder tracking reports to determine CW motion at the time of daily port films, during FB, the plateau of each DIBH, and beam-on time. We summed anterior and superior motion using the Pythagorean Theorem and report our results in this combined axis. Paired t-test was used to compare heart dose with vs. without DIBH and CW motion during plateau DIBH vs. beam-on.

RESULTS: DIBH significantly reduced MH and LAD dose vs. FB plans (MH 1.26 ± 0.51 Gy v 2.84 ± 1.55 Gy, $p < 0.01$), (LAD 5.49 ± 4.02 Gy v 18.15 ± 8.78 Gy, $p < 0.01$). DIBH CW position was a mean of 13.9 ± 5.3 mm anterior and superior to FB position. The mean difference in CW position at the time of daily port film vs. beam-on was -1.0 ± 2.5 mm. Plateau DIBH CW motion was 2.8 ± 2.3 mm, significantly increased from CW motion during beam-on (1.1 ± 1.2 mm, $p < 0.01$). Treatment was paused in 23% of fractions to adjust for suboptimal breath hold or CW position.

CONCLUSIONS: DIBH reduced the MH and LAD dose by at least 50%. Real-time tracking with electromagnetic transponders allowed us to limit treatment to the most stable portion of the DIBH plateau, significantly reducing intra-fraction motion**.** Electromagnetic confirmation of CW position allowed verification of breath-hold reproducibility.

APPENDIX 9

Abstract: Margins for Deep Inspiration Breath Hold (DIBH) With Electromagnetic Confirmation of Chest Wall Position for Adjuvant Therapy of Left Breast Cancer*

** Kathpal M, Tinnel B, Malmer C, Ninneman S, Wendt S, Hughs G, Gossweiler M, Valentich D, Sillings J, Macdonald D. (15 September 2014). Margins for deep inspiration breath hold (DIBH) with electromagnetic surface transponder confirmation of chest wall position for adjuvant therapy of left breast cancer. Poster presented at The American Society for Radiation Oncology (ASTRO) Annual Conference, San Francisco, CA.*

PURPOSE/OBJECTIVES: While DIBH is often used for radiation of left breast cancers to reduce heart dose, the combination of DIBH and electromagnetic surface transponders is new. We examined the accuracy of this combination in terms of systematic and random error to develop a theoretical necessary margin for such treatment using the technique of van Herk et al. initially derived for prostate cancer patients.

MATERIALS/METHODS: This IRB-approved study included 15 patients planned and treated with DIBH with electromagnetic surface transponders used to confirm chest wall (CW) position. After set-up and shifts, confirmatory port films were taken just prior to treatment daily. Surface transponders were used to track the position of the CW during port film and treatment. We retrospectively compared port films to planning DRRs using a reproducible auto-match technique to determine interfraction error in 3 dimensions. We then used transponder tracking reports to compare the CW position during treatment to that at the time of port film. By combining the port-film and tracking report analyses we determined positioning error for the "worst case" (using the largest error recorded for each axis on each day), and for the "most likely case" (using the error from the CW position at which the majority of the treatment was delivered each day). We then used the method of Van Herk et al., including a 2D margin formula (margin = $2.15\sum + 0.7\boldsymbol{\sigma}$), to calculate estimates of systematic and random error and margins along each axis for the "most likely" and "worst-case" situations.

RESULTS: For both "most likely" and "worst case" situations, mean**,** systematic and random error, and necessary margin for 95% coverage of 90% of patients according to 2D parameters described by Van Herk, et al. are displayed in Table 1.

CONCLUSIONS: Necessary margins for breast cancer treatment with DIBH and surface transponder tracking include a 9 mm longitudinal margin, 5 mm vertical margin, and 4 mm lateral margin. Margins required for the "worst case" did not differ significantly. Margins were predominantly determined by interfraction error.

Table 1: Errors and necessary margins ("most likely case"/"worst case")

	Lateral (LR) (mm)	Longitudinal (SI) (mm)	Vertical (AP) (mm)	
Mean error (M)	0.5 /	2.1 /	-0.5 /	
Systematic error ($\sum$)	1.2 /	2.7 /	1.4 /	
Random error($\boldsymbol{\sigma}$)	2.0 /	3.2 /	2.0 /	
Necessary margin ($2.15\sum + 0.7\boldsymbol{\sigma}$)	4.0 /	8.1 /	4.4 /	

APPENDIX 10

Abstract: Margins for Deep Inspiration Breath Hold (DIBH) With Electromagnetic Confirmation of Chest Wall Position for Adjuvant Therapy of Left Breast Cancer*

** Kathpal M, Tinnel B, Malmer C, Ninneman S, Wendt S, Hughs G, Gossweiler M, Valentich D, Sillings J, Macdonald D. (15 September 2014). Margins for deep inspiration breath hold (DIBH) with electromagnetic surface transponder confirmation of chest wall position for adjuvant therapy of left breast cancer. Poster presented at The American Society for Radiation Oncology (ASTRO) Annual Conference, San Francisco, CA.*

PURPOSE/OBJECTIVES: While DIBH is often used for radiation of left breast cancers to reduce heart dose, the combination of DIBH and electromagnetic surface transponders is new. We examined the accuracy of this combination in terms of systematic and random error to develop a theoretical necessary margin for such treatment using the technique of van Herk et al. initially derived for prostate cancer patients.

MATERIALS/METHODS: This IRB-approved study included 15 patients planned and treated with DIBH with electromagnetic surface transponders used to confirm chest wall (CW) position. After set-up and shifts, confirmatory port films were taken just prior to treatment daily. Surface transponders were used to track the position of the CW during port film and treatment. We retrospectively compared port films to planning DRRs using a reproducible auto-match technique to determine interfraction error in 3 dimensions. We then used transponder tracking reports to compare the CW position during treatment to that at the time of port film. By combining the port-film and tracking report analyses we determined positioning error for the "worst case" (using the largest error recorded for each axis on each day), and for the "most likely case" (using the error from the CW position at which the majority of the treatment was delivered each day). We then used the method of Van Herk et al., including a 2D margin formula (margin = $2.15\sum + 0.7\boldsymbol{\sigma}$), to calculate estimates of systematic and random error and margins along each axis for the "most likely" and "worst-case" situations.

RESULTS: For both "most likely" and "worst case" situations, mean**,** systematic and random error, and necessary margin for 95% coverage of 90% of patients according to 2D parameters described by Van Herk, et al. are displayed in Table 1.

CONCLUSIONS: Necessary margins for breast cancer treatment with DIBH and surface transponder tracking include a 9 mm longitudinal margin, 5 mm vertical margin, and 4 mm lateral margin. Margins required for the "worst case" did not differ significantly. Margins were predominantly determined by interfraction error.

Table 1: Errors and necessary margins ("most likely case"/"worst case")

	Lateral (LR) (mm)	Longitudinal (SI) (mm)	Vertical (AP) (mm)	
Mean error (M)	0.5 /	2.1 /	-0.5 /	
Systematic error ($\sum$)	1.2 /	2.7 /	1.4 /	
Random error($\boldsymbol{\sigma}$)	2.0 /	3.2 /	2.0 /	
Necessary margin ($2.15\sum + 0.7\boldsymbol{\sigma}$)	4.0 /	8.1 /	4.4 /	

APPENDIX 11

Abstract: Differences between beacon-localized and cone-beam CT (CBCT)-localized radiation therapy to the prostatic fossa.*

** Kathpal M, Brand T, Ninneman S, Hughs G, Katz L, Brown M, Halligan J, Brooks J, Macdonald D, Tinnel B. (22-25 September 2013). Differences between beacon-localized and cone-beam CT (CBCT)-localized radiation therapy to the prostatic fossa. Poster presented at the ASTRO 2013 Annual Conference, Atlanta, GA.*

PURPOSE/OBJECTIVES: Either CBCT or electromagnetic beacon transponders can localize the prostatic fossa for adjuvant or salvage radiation therapy. We hypothesize that beacons localize this isocenter differently than CBCT. We sought to test this hypothesis, and to evaluate if the beacon-localized isocenter more closely aligns the clinical target volume (CTV) with daily changes in rectum and bladder position such that planning target volume (PTV) margins may be reduced.

MATHERIALS/METHODS: 12 patients requiring post-prostatectomy radiation were treated on this IRB-approved prospective study. Each patient had 3 beacons placed in the prostatic fossa; one to the right of the vesico-urethral anastomosis and two others in the location of the left and right prostate pedicles adjacent to the removed seminal vesicles. Daily radiation was localized by beacons and a CBCT was taken for analysis. By measuring differences between the CTV and relevant anatomy on 5 equally-spaced axial CT slices we calculated necessary PTV margins for each fraction. We then auto-fused each CBCT scan with the treatment planning scan, recorded the shifts incurred, and repeated our measurements, representing a hypothetical CBCT -localized treatment. We report a PTV margin for each technique that would cover the CTV during 95% of all 379 fractions analyzed. We also used intra-fraction motion data (considering anterior motion to coincide with anterior movement of the posterior bladder wall) to produce a worst-case estimate of required anterior PTV margins.

RESULTS: When shifting from the beacon-localized isocenter to the CBCT-localized isocenter, the mean vertical patient shift for all 379 fractions was 1.3 mm ant (SD 2.9 mm, range 5 mm post to 10 mm ant). The mean longitudinal shift was 2.2 mm sup (SD 3.1 mm, range 7 mm inf to 12 mm sup). The mean lateral shift was 0.3 mm to the left (SD 1.5, range 13 mm left to 4 mm right). For beacon-localized treatment, maximum necessary PTV margins were 10 mm ant, 12 mm post, and 6 mm lat. Incorporating measured intra-fraction motion, the anterior margin would be increased to 11 mm. For CBCT-localized treatment, maximum necessary PTV margins were 18 mm ant, 8 mm post, and 6 mm lateral. Inclusion of intra-fraction motion did not change the necessary anterior margin for CBCT-localized treatment. Intra-fraction motion exceeded tracking limits of 5 mm (corrected with treatment pause or reposition) in 13% of fractions.

CONCLUSIONS: In our cohort, beacon localization placed the isocenter (on average) anterior and superior to the CBCT isocenter, with significant variation over the entire group. The beacon-localized isocenter accounts for some changes in bladder position, thus allowing a decreased anterior PTV margin, or decreased amount of the posterior bladder included in the CTV.

APPENDIX 12

Abstract: Inter-fraction displacement of electromagnetic beacons in patients receiving post-prostatectomy radiation therapy. *

** Kathpal M, Brand T, Ninneman S, Hughs G, Smith A, Brooks J, Halligan J, Malmer C, Tinnel B, Macdonald D. (22-25 September 2013). Inter-fraction displacement of electromagnetic beacons in patients receiving post-prostatectomy radiation therapy. Poster presented at the ASTRO 2013 Annual Conference, Atlanta, GA.*

PURPOSE/OBJECTIVES: Optimally using beacon transponders during radiation therapy to the prostatic fossa requires understanding daily variations in the spatial relationships of the three beacons with each other and surrounding target areas. In a beacon-localized post-prostatectomy radiation therapy cohort we sought to understand variation in beacon geometry and location by tracking each beacon's daily position within the coordinate system of the planning CT.

MATERIALS/METHODS: 12 patients on an IRB-approved prospective study had treatments localized by beacon transponders, and a daily cone-beam CT (CBCT) taken for position verification. Each CBCT was retrospectively auto-matched to the treatment planning CT using a reproducible algorithm. We recorded the location of each beacon within the auto-matched CBCT coordinate system, making the assumption that this accurately reflected the planning CT coordinate system. We then quantified inter-fraction beacon displacement over a total of 379 fractions. We also measured daily differences between each beacon's planned and actual distance from each other beacon in each axis.

RESULTS: Mean inter-fraction beacon displacements in mm (with standard deviation (SD) in mm) are displayed in Table 1. Mean daily differences from plan in distance between beacons were all less than 1 mm in each axis, but SD varied significantly. In the lateral axis, these differences for all beacons had a SD of 2.0 – 2.4 mm. For the R base and L base beacons these differences in all axes had a SD of 1.9 – 2.0 mm. In contrast, the difference from plan in distance between either base beacon and the apex beacon in the sup/inf or ant/post axis had a SD of 3.1 – 3.4 mm.

CONCLUSIONS: On average beacons moved 0.2 – 2.0 mm superior and anterior from the planned location during radiation therapy, but this was overshadowed by a large SD representing significant random motion. The difference from plan in the distance between each base beacon and the apex beacon also varied significantly in the sup/inf and ant/post axes. These beacon displacements likely reflect daily changes in bowel and bladder position - we are currently studying their clinical significance.

Table 1: Mean inter-fraction beacon motion in mm with SD.

Beacon	Sup/Inf Axis	Ant/Post Axis	Left/Right Axis
Apex	1.3 sup SD 2.6	0.8 ant SD 2.6	0.1 left SD 1.3
L Base	1.9 sup SD 3.9	1.0 ant SD 3.8	0.4 right SD 1.5
R Base	2.0 sup SD 4.0	0.2 ant SD 4.1	0.0 left SD 1.9

APPENDIX 13

Abstract: The use of electromagnetic transponder beacons to reduce planning target volume (PTV) margins in post-prostatectomy patients undergoing adjuvant or salvage radiation therapy. *

** Kathpal M, Ninneman S, Huang R, Wendt S, Malmer C, Brand T, Halligan J, Brooks J, Brown M, Tinnel B, Macdonald D. (14-16 February 2013). The use of electromagnetic transponder beacons to reduce planning target volume (PTV) margins in post-prostatectomy patients undergoing adjuvant or salvage radiation therapy. Poster presented at the ASCO/ASTRO 2013 Genitourinary Cancers Symposium, Orlando, FL.*

** Kathpal M, Ninneman S, Huang R, Wendt S, Malmer C, Brand T, Halligan J, Brooks J, Brown M, Tinnel B, Macdonald D. (2013, April). The use of electromagnetic transponder beacons to reduce planning target volume (PTV) margins in post-prostatectomy patients undergoing adjuvant or salvage radiation therapy. Oral presentation given at Madigan Army Medical Center's Annual Research Day, Tacoma, WA.*

BACKGROUND: We determined necessary PTV margins when beacons are used to localize the prostatic fossa in post-prostatectomy patients. We hypothesized beacon localization would allow for decreased PTV margins and increased normal tissue sparing.

METHODS: 10 patients requiring post-prostatectomy radiation were treated on this IRB-approved prospective study. Each patient had 3 beacons placed in the prostatic fossa. Daily radiation was localized by beacons and a cone-beam CT (CBCT) taken for analysis. By measuring differences between the treated clinical target volume (CTV) and relevant anatomy on 5 equally-spaced axial CT slices we calculated necessary PTV margins for each fraction. We then auto-fused each CBCT scan with the treatment planning scan, recorded the shifts incurred, and repeated our measurements, representing a hypothetical CBCT - localized treatment. We report a PTV margin for each technique that would cover the CTV during 90% of all 304 fractions analyzed. We also used intra-fraction motion data to produce a worst-case estimate of required PTV bladder margins.

RESULTS: The average shifts from the beacon to CBCT- localized isocenter were 2.9, 3.2, 1.0 mm and 0.58 degrees in the vertical, longitudinal, lateral, and rotational planes, respectively. Necessary PTV margins for beacon and CBCT localization are listed in Table 1.

CONCLUSIONS: Beacon localization "attaches" the CTV to the bladder, allowing a decrease in PTV margin or the amount of posterior bladder included in the CTV. This could lead to decreased rates of bladder toxicity.

Table 1: Necessary PTV margins based on 90th percentile of 304 fractions analyzed

					Necessary PTV margins				
Axial CT slice location and reference structure	**Direction**				**Without intra-fraction motion**			**With intra-fraction motion**	
	ANT	POST	LT	RT	BEACONS (mm)	CBCT (mm)		BEACONS (mm)	CBCT (mm)
INFERIOR									

Symphysis pubis	X				3	6			
Ant rectal wall		X			9	7			
INFERIOR-MID									
Symphysis pubis	X				3	6			
Ant rectal wall		X			7	5			
MIDDLE									
Symphysis pubis	X				3	6			
Ant rectal wall		X			5	3			
Left obt internus			X		4	4			
Right obt internus				X	5	3			
SUPERIOR-MID									
Post bladder wall	X				7	12		8	13
Ant rectal wall		X			7	2			
SUPERIOR									
Post bladder wall	X				8	15		8	15
Ant rectal wall		X			9	6			

APPENDIX 14

Abstract: Anorectal Angle is Associated with Bowel Toxicity One Month Following Radiation Therapy for Prostate Cancer *

** Gossweiler M, Waggoner A, Huang R, Ninneman S, Hughs G, Wendt S, Brown M, Tinnel B, Macdonald D. (8-9 February 2013). Anorectal angle is associated with bowel toxicity one month following radiation therapy for prostate cancer. Poster presented at the ASTO/RSNA 2013 Cancer Imaging and Radiation Therapy Symposium, Orlando, FL.*

* Gossweiler M, Waggoner A, Huang R, Ninneman S, Hughs G, Wendt S, Brown M, Tinnel B, Macdonald D. (2013, April). Anorectal angle is associated with bowel toxicity one month following radiation therapy for prostate cancer. Oral presentation given at Madigan Army Medical Center's Annual Research Day, Tacoma, WA.

PURPOSE/OBJECTIVES: Bowel toxicity following radiation therapy (XRT) for prostate cancer can cause a significant decrease in patient quality of life. Some of this toxicity - such as rectal bleeding - seems to relate directly to damage to the rectal wall, while other elements of bowel toxicity - such as urgency, frequency, or fecal leakage - may be related to anal canal geometry and musculature. The anorectal angle (ARA) and the volume of the puborectalis muscle (VPRM) - which assists in maintaining the anorectal angle - are two image-based measurements which are known to be related to the maintenance of fecal continence. Here we explore whether a large pre-treatment ARA or a small VPRM are associated with increased bowel toxicity following XRT.

MATHERIALS/METHODS: We studied 10 consecutive patients with low-to-intermediate risk prostate cancer treated on a prospective study with definitive intensity-modulated radiation therapy (IMRT). All patients completed the EPIC quality of life questionnaire at the end of treatment, and at 1 and 4 months post-treatment. We used the patients' answers on the bowel section of these questionnaires to divide the patients into two groups: one with few side effects as reflected by a score within 10% of the most favorable score possible, and the other with more side effects as reflected by a lower score. The patients' VPRMs were measured by contouring on planning CT scans. The anorectal angle was measured on sagittal CT scan reconstructions as the angle between the line down the center of the long axis of the anal canal, and the line down the center of the long axis of the rectum immediately superior to the anal canal. Both the VPRM and the ARA measurements were then categorized as "small" or "large" using the mean as the dividing line. We used Fisher's exact test to evaluate for a significant association between ARA and bowel toxicity and between VPRM and bowel toxicity.

RESULTS: EPIC bowel toxicity scores varied from a low of 56.7 to a high of 100, with a mean of 83.8 and standard deviation of 14.76. VPRM varied from 6.45cc to 15.87cc (std. dev. 3.13), and was not associated with bowel toxicity ($p = 1.000$ at all time points). ARA varied between 93.5 and 121.8 deg (std. dev. 9.69), and was correlated with bowel toxicity one month following completion of therapy ($p = 0.048$), but not at the end of XRT ($p = 1.000$) or at 4 months post-treatment ($p = 0.524$).

CONCLUSIONS: These results are hypothesis-generating and based on a very small sample size. Further evaluation of the association of ARA with bowel toxicity following XRT for prostate cancer in a larger cohort is warranted. If there is an association between baseline ARA and bowel toxicity, measuring the ARA on a pre-treatment CT scan could allow more informed counseling of patients regarding the risks for bowel toxicity following XRT.

APPENDIX 15

Abstract: Dose to the muscles of fecal continence during radiation therapy for prostate cancer. *

**Waggoner A, Brown M, Tinnel B, Halligan J, Brand T, Brooks J, Ninneman S, Hughs G, Macdonald D. (2-4 February 2012). Dose to the muscles of fecal continence during radiation therapy for prostate cancer. Poster presented at the ASCO/ASTRO/SUO 2012 Genitourinary Cancers Symposium, San Francisco, CA.*

INTRODUCTION AND OBJECTIVE: Radiation therapy for prostate cancer can lead to loss of fecal continence; our understanding of the dose-volume relationships of this late toxicity continues to develop. The external anal sphincter (EAS), internal anal sphincter (IAS), the puborectalis (PRM), the pubococcygeus (PCM), and the illiococcygeus (ICM) muscles all contribute to fecal continence. We developed a reproducible method for contouring these muscles and in this preliminary study evaluate whether decreased planning target volume (PTV) margins lead to potentially clinically significant decreases in dose to these muscles during definitive radiation therapy for prostate cancer.

METHODS: Muscles involved in fecal continence were contoured for 10 consecutive patients on a prospective study of reduced PTV margins for treating low-to-intermediate risk prostate cancer with intensity modulated radiation therapy (IMRT) using an electromagnetic localization system. IMRT plans to a prescribed dose of 7740 cGy were developed using 10mm PTV margins (5mm posteriorly), and compared with actual treatment IMRT plans using 3mm circumferential PTV margins. Decreases in dose were evaluated for statistical significance using an unpaired t-test.

RESULTS: Reducing PTV margins decreased the mean PTV volume from 176.2 ml to 91.9 ml. Mean doses to the EAS, IAS, and rectum (REC) decreased significantly; from 11.0 Gy to 4.1 Gy ($p=0.005$), from 30.5 Gy to 15.0 Gy ($p = 0.004$), and from 43.7 Gy to 35.6 Gy ($p=0.006$) respectively. Decrease in the mean dose to the PRM was nearly statistically significant, 48.7 Gy to 34.6 Gy ($p = 0.055$). Decreases in mean doses to the PCM and ICM were not statistically significant; from 61.9 Gy to 55.2 Gy ($p = 0.107$), and from 40.7 Gy to 34.8 Gy ($p = 0.176$), respectively.

CONCLUSIONS: Using electromagnetic tracking to reduce PTV margins leads to a significant decrease in dose to the muscles of fecal continence, with mean dose decreases in a range that may be clinically significant.